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Bronchogenic Carcinoma*

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Less than a half century ago cancer of the lung was such a rarity that when a case was encountered, it was reported. Weller,[40] in 1913, was able to collect from the world literature only 89 authenticated cases and reported one which he had observed at autopsy. Adler, in 1912, stated: "There is complete consensus of opinion that primary malignant neoplasms of the lung are among the rarest form of disease."[1] McMahon and Carman,[31] in 1918, reported 5 cases from the Mayo Clinic and were able to collect 428 cases.

Incidence. Although cancer of the lung was an extremely rare lesion 50 years ago, it has become the most frequent cancer and now supersedes cancer of the breast. In Massachusetts, lung cancer increased from 3.08 per 100,000 population in 1930 to 42.16 in 1955, and during this period of time breast cancer increased from 29 to only 36 per 100,000 population.[29] From 1931 to 1950 in New York State, it increased 385 per cent in men and 68 per cent in women. During this time, all other cancers increased only 2 per cent in men and decreased 15 per cent in women.[28] The number of deaths from the disease in the United States in 1930 was: 2,500; in 1950, 18,000 and in 1956, 29,000. In Switzerland, it increased 32 fold from 1900 to 1952, and during this time the population increased only 1.4-fold, all deaths 0.8-fold, and all cancer death 1.9-fold.[17] In Finland, lung cancer increased approximately 7 per cent each year from 1936 to 1943, after which time the annual increase became approximately 13 per cent.[25] Also since the early 1900's the per capita consumption of tobacco in Finland has been higher than in any other European country. Similar results have been reported by Denoix and Gelle[10] in France. In England, lung cancer increased 38-fold in men from 1920 to 1954,[30] and in Holland[26] 24-fold in men and ten-fold in women from 1924 to 1951. In Austria, lung cancer represented 1.6 per cent of all cancer in 1920, 2.2 per cent in 1930, and 10 per cent in 1956. Clemmesen[8] stated that in Copenhagen in the 1985-1990 period, lung cancer deaths in men will equal all cancers in 1950. He further referred to the incidence of bronchogenic carcinoma as being pandemic and warned that unless young persons are prevented from acquiring smoking habits, we will not be able *to avoid one of the major catastrophes in medical history.*[7]

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Although it is contended that the increased incidence is apparent only because of better recognition and diagnosis, such is certainly not the case because of the increased incidence in autopsy studies. Wegelin[39] reported a progressive increase in the incidence in the autopsies at the Bern Pathological Institute from 2.5 per 100,000 autopsies in the period 1900-1904 to 14.2 in the period 1935-1939. Matz[32] found that the incidence of bronchogenic carcinoma to all carcinomas as determined by autopsy in the Veterans Bureau Hospitals increased from 6.4 per cent for the period 1927 to 1931; to 15.8 per cent for 1932-1937; to 23.4 for the year 1957. Clemmesen,[7] an eminent pathologist in Denmark, who is extremely interested in the epidemiology of cancer, is convinced from his study of the Cancer Registry in Denmark that the increased incidence is real and not relative. He stated: "It seems impossible to escape the conclusion that from the studies reported we are now facing the beginning of one of the major catastrophes in medical history, a mortal disease which demands decades for its development and probably as lengthy efforts for its prevention." O'Neal and his coworkers[35] found that the incidence at the Barnes Hospital in St. Louis increased from 1.1 per cent of all autopsies in 1910-1919 to 4.2 per cent in 1930-1939, and to 7.8 per cent in 1945-1954. We agree with their conclusions that the increased incidence is real and not relative.

Any lesion that has increased as much as bronchogenic cancer must be seriously considered and steps taken to control and, if possible, prevent it. A lead concerning the cause of the tremendous increase is that until the midthirties it involved men and women with equal frequency. However, since then, although there has been a slight but continued increase in women, the increase in men has been alarming. The unprecedented increase in the incidence of bronchogenic cancer is undoubtedly due to the carcinogenic effect of cigarette smoking, which accounts for the alarming increase in the midthirties. During World War I, cigarette smoking in men increased considerably and the 20-year lag between 1914 and the midthirties was the length of time necessary for the effect of the cancer-producing agent in cigarettes to become evident.

It has been suggested by many that the increase in bronchogenic cancer is a result of contaminants in the air, such as smog, and that lung cancer is frequent in London because of excessive smog. However, in Denmark, a bare 30 miles away, where the incidence of cancer of the lung is approximately the same as in England, and where the incidence of cancer of the lung is almost identical, there is no smog. According to the United States Public Health Statistics, the incidence of cancer of the lung is higher among the citizens of New Orleans than among those of Pittsburgh. Although Pittsburgh now has a smog-control program, 25 or 30 years ago such was not the case; and if smog were a factor, the incidence should be considerably higher there than in New Orleans. Also, if smog were a factor, it would be difficult to explain why the incidence of cancer of the lung has increased so much more in men than in women, or would the nonbelievers have us think that women breathe purer air than men? A study by Stocks and Campbell[38] suggests, however, that air contamination may act as an additive factor to smoking in causing lung cancer.

Because of the fallacious concept that women now smoke as much as men, it is frequently contended that if smoking were an etiologic fac-

tor in bronchogenic cancer, it should be as frequent in women as in men. A considerable lag period is required for a carcinogen to cause cancer. This naturally means that the incidence of smoking in both sexes should have been the same 25 years ago, which, of course, is not true. Even at the present time, many more men than women smoke. According to the Public Health Statistics, 67 per cent of the women in the United States and only 23 per cent of the men are non-smokers.

As mentioned previously, bronchogenic cancer is extremely common in England; in fact, even more common than in the United States. In 1953, in England, of all men who died between the ages of 45 and 55 years (the most productive period of a man's life) 10 per cent died of cancer of the lung.[11] The death rate is higher in Great Britian than in any other country. This has been offered as proof that there can be no causal relationship between smoking and cancer of the lung, because we in the United States smoke more than the British. This, however, is only a half truth, because although we smoke more now than the British, our smoking has been greater than theirs for the past 10 years only. Until that time, the British smoked a great deal more than we, and they are now paying the dreadful price for their excessive smoking these past 25 years. It is horrifying to envision the future in this country when, in another 10 or 15 years, our smoking habits catch up with us.

Although it is generally accepted by most people at the present time that there is a causal relationship between cigarette smoking and cancer of the lung, there are some who are unwilling to accept the relationship. However, I have yet to see a physician who will not admit such relationship unless he is an employee of a tobacco company or is addicted to tobacco. The evidence supporting the causal relationship is of two types: (1) statistical and (2) experimental. The evidence in both these categories supports the contention that there is a causal relationship between the two. As mentioned previously, cancer of the lung is increasing more than any other cancer in the body and at the present time it is the most frequent cancer, having exceeded all others, including that of the breast. The parallelism between the increased incidence of bronchogenic cancer and the consumption of cigarettes has also been referred to as well accepted by most observers. Clemmesen[8] stated: "Based on detailed statistical studies it has been found that several European countries show an almost linear association between cigarette consumption about 1930 and lung cancer mortality about 1950." Gsell[17] found that the lung cancer increase in Switzerland was proportionate to the amount smoked.

Of all the patients with lung cancer, 85 per cent smoked 15 or more cigarettes a day as compared with the control in which only 32 per cent smoked this much.

Herbich and Neuchold[22] also found a relationship between the amount smoked and the incidence of bronchogenic cancer in Austria. In Vienna, where the lung cancer mortality rate was highest, 450 per 100,000 population, the annual per capita consumption of tobacco was 1,129 whereas in Burgenland, where the lung cancer incidence was 90 per 100,000, the annual per capita consumption of cigarettes was 558. Percy Stocks,[37] in the Annual Report of the British Empire Cancer Campaign in 1957, in quoting the relationship between smoking and cancer stated: "The death rates of pipe smokers are one-and-one-half to four-and-one-half times those

of non-smokers; those of men who had smoked fewer than 100 cigarettes per week are three to five times the rate of non-smokers, and the ratios increase with rising cigarette consumption to six to 15 times the non-smokers rate amongst those who had smoked 20 or more per week."

Doll and Hill[12] in a statistical study among physicians in England, obtained similar findings. The incidence of lung cancer was as follows: non-smokers 7 per 100,000; pipe smokers, 38; pipe and cigarette smokers, 68; and cigarette smokers, 125. Of the cigarette smokers the incidence was 1 to 14 cigarettes daily, 47; 15 to 24 cigarettes, 86, and more than 25 cigarettes, 166. Delarue[9] in France, is equally convinced of the causal relationship between smoking and cancer. He stated, "The evidence to support this thesis is sufficiently definite that cigarette manufacturers now have a moral obligation to attempt to prove or disprove its validity and to eradicate any carcinogenic agent from their product when and if it is isolated."

The Norwegian Government is so convinced of the causal relationship between smoking and lung cancer that they forbid the sale of tobacco to minors and 0.1 per cent of the government's tobacco revenue is allocated for research on the deleterious effects of tobacco.[2]

The Medical Research Council of Great Britain,[33] a government agency, recently drew the following conclusions after extensive investigations over a period of five years: "Evidence from many investigations in different countries indicates that a major part of the increase (of lung cancer) is associated with tobacco smoking particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect. The identification of several carcinogenic substances in tobacco smoke provides a rational basis for such causal relationship."

The British government also has posted in all public places large yellow posters with the following inscription: "To all Smokers! There are now the strongest reasons to believe that smokers—particularly of cigarettes—run a greater risk of lung cancer than non-smokers. The more cigarettes consumed, the greater the risk."

In the United States two very important prospective statistical studies, both of which comprised about 200,000 men each, have been made, one by the American Cancer Society[21] and the other by the Veterans Administration.[15] The lung cancer deaths per 100,000 population in the American Cancer Society study conducted by Hammond and Horn[21] were, non-smokers, 3.4; less than one-half pack of cigarettes daily, 51.4; one-half to a pack, 59.3; 1-2 packs, 144; and over 40 cigarettes, 217. The deaths from lung cancer per 100,000, as reported by Dorn[15] from a study among veterans 40 to 54 years of age, were: non-smokers, 9.5; pipe smokers, 13.8; cigar smokers, 17.8 and cigarette smokers, 25.7. Among the cigarette smokers the deaths were: less than 10 cigarettes daily, 29; 10 to 20 cigarettes, 66; 21 to 39 cigarettes, 77, and more than 40 cigarettes, 99. Although these studies were made in men, because lung cancer is much more common in men than in women the incidence in women is also dependent upon the amount smoked, as reported by Haenszel and Shimkin.[18] They[19] found that cancer of the lung was 1.6 times higher in the occasional cigarette smokers or those who had discontinued smoking than in the non-smokers, in those who smoked 20 or less cigarettes a day it was increased

2.3 times, and in those who smoked more than 20 cigarettes, 7.1 times. Similar results are reported by Wynder and associates.[41]

The consumption of cigarettes in the United States increased progressively from an annual per capita consumption of 16 in 1880 in all persons 15 years of age and older to 3,556 in 1953. However, it did decrease to 3,195 in 1956. The incidence of cancer of the lung can be expected to increase even more because more young people are smoking now than 25 to 30 years ago. The American Cancer Society study showed that in the older group, those 65 to 69, 21.6 per cent of the men interviewed had never smoked and only 20.3 per cent had smoked more than a pack a day, whereas in the younger age group (50 to 54) only 15 per cent had never smoked and 43 per cent had smoked a pack or more a day. In a recent poll of teenagers, it was found that of those 13 to 15 years of age, 37 per cent smoked cigarettes whereas of those from 16 to 19 years of age, inclusive, 67 per cent smoked cigarettes.

At a meeting of the Committee on Cancer of the Lung of the American Cancer Society, about 10 years ago, a statement was made that there could be no causal relationship between smoking and cancer of the lung because if there were, precancerous lesions should be seen in the tracheobronchial tree. This statement distressed me until I discussed it with Dr. Charles Dunlap, Professor of Pathology at the Tulane University School of Medicine, and he told me that it was not customary to examine the bronchial mucosa carefully to determine whether precancerous lesions are present. Following this, Dr. Guillermo Carrera and Dr. M. Costilow,[5] who was then a senior medical student at Tulane University, began an investigation that was never published. They found that changes in the bronchial mucosa varied according to the amount smoked, that the tracheobronchial mucosa of non-smoking men 50 years of age, examined at autopsy, showed very little change, that in moderate smokers there was hyperplasia and thickening of the mucous membrane, and in heavy smokers, not only extensive metaplasia but also carcinoma *in situ* and early invasive carcinoma. This work was subsequently corroborated in a much more extensive investigation by Auerbach and his associates.[3, 4] These investigators found that changes in the tracheobronchial mucous membrane varied according to the amount smoked and the bronchial mucosa in heavy cigarette smokers exhibited basal cell stratification, squamous metaplasia and carcinoma *in situ*. Similar results have been reported by Chang.[6]

Supporting the contention that cigarette smoking is a causal factor in bronchogenic cancer is not only the above mentioned evidence of changes in the bronchial mucosa varying with the amount smoked and the statistical evidence that the incidence of lung cancer increases with increased smoking, but also the statistical evidence that the tendency to develop lung cancer diminishes after discontinuance of smoking. Hammond and Horn[21] in the American Cancer Society study showed that although the lung cancer death rate per 100,000 population was 3.4 among non-smokers, it was 57.6 among those who smoked less than a pack a day and who continued smoking. Among those who had stopped less than 10 years, it was 35.5 and among those who stopped over 10 years it was 8.3. However, in the group that had smoked more than a pack a day, it was 157.1. Among those who continued smoking, 77.6, if they had stopped from one to 10

years, and 60.5, if they had stopped over 10 years. Similar results were obtained by Doll and Hill,[13] who found an incidence of 103 in those who continued smoking, 59 in those who had discontinued less than ten years, 35 in those who had discontinued more than 10 years as compared with 7 among those who had never smoked.

Experimental work supporting a relationship between smoking and cancer of the lung consists of the demonstration of carcinogenic effect of tobacco smoke. In 1943, Roffo[36] produced cancer in animals by applying tobacco tar to the skin of the animals. Wynder and associates[42] showed that the tar, obtained from the smoking of cigarettes in a way comparable to human smoking, when applied to the skin of animals three times a week produced one benign tumor at the end of eight months and one true cancer at the end of a year, and at the end of two years 44 per cent of the animals developed, at the site of the application of the tar, a cancer that metastasized and killed the animals. In a control group in which only the solvent was applied to the skin of the animals, not one animal developed either a benign or malignant tumor at the end of two years. Essenberg and his associates[16] were able to produce bronchogenic neoplasms by subjecting animals to cigarette smoke. Leuchtenberger and associates[27] showed that in mice subjected to cigarette smoke there were changes in the bronchi that varied from bronchitis with mild proliferative epithelial changes to those with atypical basal cell hyperplasia, squamous cell hyperplasia, and even carcinoma *in situ*.

The demonstration of carcinogens in the smoke from cigarettes explains why cancer of the lung is increasing and why it is found, with the exception of adenocarcinoma, particularly only in those who smoke and smoke heavily and that the incidence varies with the amount smoked.

Hilding,[23, 24] has demonstrated from extensive experimentation that a great deal of the tar drawn into the lung during smoking remains in the lung. Using fresh lungs from cows and pulling the smoke through the bronchi as a human being does when he smokes, tar is deposited in droplets in the trachea and bronchi. The cilia tend to move the tarred particles upward, but smoking definitely decreases ciliary action. He found that the quantity of smoke delivered to the lung was proportionate to the length of the puff and the amount of pressure used and when the action of the cilia was interfered with concentration of the tar remained in certain areas.

Because the number of persons smoking is much greater today than it was 25 years ago, it can be predicted that the incidence of cancer of the lung will increase sharply for at least the next 20 to 25 years, when the carcinogenic effect of tobacco among those now smoking will become effective. It behooves the medical profession, therefore, to be constantly on the alert to detect bronchogenic cancer early in its development so that therapeutic measures can be undertaken to correct the condition.

We have had a total of more 1,500 cases of bronchogenic cancer, of which 875 have been seen and treated in the Ochsner Clinic from January 1, 1942 to December, 1957. These are all private patients and, therefore, are in a better economic status than the other patients who were seen and treated at the Charity Hospital. Of the 875 private cases, 769 (88 per cent) were men and 106 (12 per cent) were women.

The reason for the higher incidence in men is that men smoke more

than women although the incidence is increasing in women. If women ever smoke as much as men, the incidence in women will approximate that in men, because as shown by Haenszel and Shimkin[18, 19] and Wynder,[41] the incidence in women varies with the amount smoked.

Pathology. Bronchogenic cancer involves both lungs of the body with equal frequency. In our present series, the right lung was involved in 53.4 per cent and the left lung in 46.6 per cent. The upper lobes are primarily involved, because during inhalation of smoke the greatest concentration is in the upper lobes. The two upper lobes were involved with equal frequency, 27 per cent each. The right main bronchus was involved in 4 per cent and the left main bronchus in 6 per cent. The intermediate bronchus on the right was involved in 1 per cent, the middle lobe on the right in 5 per cent, the lower lobe on the right in 17 per cent, and the lower lobe on the left in 13 per cent. In those cases in which the location of the tumor could be determined, it was found in the main stem bronchus in 9 per cent, in the lobe bronchus in 61 per cent, and in the periphery in 30 per cent. This varies some from our results in the series in which the Charity Hospital cases were included in which the lobe bronchus was involved in 69 per cent and the periphery in 22 per cent.

Epidermoid carcinomas were most frequent (52 per cent), 29 per cent were undifferentiated and 19 per cent were adenocarcinomas. We are of the opinion that in adenocarcinoma there is no relationship to smoking. This contention is borne out by the fact that the incidence of adenocarcinoma decreased with advancing age from 21 per cent in patients less than 50 years of age to 12 per cent in those patients over 70 years of age. We believe that adenocarcinoma develops on the basis of preexisting epithelial rest, which is congenital, and therefore, if cancer develops it should at an earlier age. Contrariwise, the incidence of epidermoid carcinoma, which we are convinced is caused by the carcinogens in tobacco smoke, increased with advancing age from 44 per cent in patients less than 50 years of age to 73 per cent in those over 70.

As has been observed previously, the histologic type of tumor varies according to the sex. This is largely because men smoke more than women, and therefore, epidermoid tumors which are largely the result of smoking occur more frequently in men. Fifty-four per cent of the men had epidermoid carcinoma and 33 per cent of the women. Men and women had undifferentiated carcinoma in about equal numbers, 29 and 26 per cent, respectively, but adenocarcinoma was found much more frequently in women than in men, 41 per cent and 16 per cent, respectively.

Diagnosis. Carcinoma of the lung begins insidiously. For this reason, there is usually considerable delay in making a diagnosis. Because of the difficulty of making a diagnosis, it is the obligation of the physician to suspect bronchogenic cancer in every heavy smoker with an obscure respiratory complaint. We believe that a history of smoking is of real diagnostic importance. In fact, it is one of the best diagnostic criteria. Approximately seven years ago we made the statement that a pulmonary lesion which might be malignant in a non-smoker is either adenocarcinoma or is not malignant. In the time which has elapsed since that statement was made it has been proved wrong in only three instances. There is no other diagnostic criterion that is so accurate as this one.

Cough is seen is most cases of bronchogenic carcinoma, but unfortunately

the heavy smoker has a chronic cough and, for this reason, it is likely to be disregarded. Wheezing, particularly in an individual who previously had not wheezed, is significant. A history of a previous respiratory tract infection, which is frequently diagnosed as viral pneumonitis because it is an atypical pneumonitis, should make one suspicious. In the present series of cases, cough was present in 85 per cent, weight loss in 60 per cent, chest pain in 58 per cent, hemoptysis in 46 per cent, dyspnea in 45 per cent, respiratory infection in 42 per cent, weakness in 39 per cent, wheezing in 20 per cent, chills and fever in 14 per cent, night sweats in 7 per cent, voice change caused by recurrent laryngeal nerve paralysis in 4 per cent, and dysphagia in 3 per cent.

The diagnosis is usually not difficult if a physician will only consider the possibility of bronchogenic carcinoma and will institute diagnostic procedures either to confirm or to exclude the presence of the lesion. By far one of the best methods of making a diagnosis because of the ease with which it can be performed is careful roentgenography of the chest. However, roentgen diagnosis is only presumptive. Bronchoscopy should be done in most instances, but it is of little or no value in peripherally located lesions and in many cases in which the lesion is located "around the corner," in the upper lobes which are not visible. However, bronchoscopy frequently gives considerable information concerning operability by determining evidence of carinal involvement. In only one-third of our cases was it possible to make a positive diagnosis by bronchoscopy so that negative bronchoscopy in no way excludes the diagnosis of bronchogenic carcinoma. Examination of sputum obtained either by coughing or by bronchial aspiration is an extremely valuable diagnostic method. In 67 per cent of our cases we were able to make a positive diagnosis by this method. A higher percentage of positive diagnoses was obtained by repeated sputum examinations than by bronchoscopic aspiration, because in the former it was possible to examine many more specimens. The sputum must be obtained from deep within the bronchi and expectorated into a receptacle containing alcohol so that the cells will be fixed immediately. In approximately 20 per cent of cases a positive diagnosis cannot be made until thoracic exploration.

Treatment. It is uniformly agreed that at the present time the only curative treatment for bronchogenic cancer is surgical extirpation. However, there is considerable controversy concerning the best type of resection. There is an increasing tendency to employ less radical procedures than previously in order to save as much pulmonary tissue as possible. It has been our contention for some time that, if at all possible, a radical en bloc excision of the entire lung and mediastinal nodes should be done, provided the previously performed pulmonary function studies indicate that the patient can tolerate such a procedure. Obviously, if the pulmonary function studies indicate that a pneumonectomy cannot be tolerated, a procedure that can be tolerated should be done. In our experience the operability and resectability rates have fluctuated throughout the years, and unfortunately, in recent years have become less. From 1941 to 1950 the operability rates varied from 64 per cent to 76 per cent and the resectability rates varied from 37 per cent to 48 per cent. However, beginning in 1950, the operability and resectability rates both decreased to reach an all time low of only 44 per cent and 32 per cent, respectively,

in the present series in 1954-1955. This decrease in operability and resectability incidences in 1954 was undoubtedly due to a delay in diagnosis, because the lesion was incorrectly diagnosed as viral pneumonitis and treated for months without the real condition being suspected. Although it is true that the pneumonitis associated with bronchogenic neoplasm is an atypical pneumonitis as viral pneumonitis is, it is our belief that a heavy smoker who develops atypical pneumonitis is more likely to have bronchogenic cancer than viral pneumonitis. The possibility of bronchogenic cancer must be considered and the diagnosis either confirmed or excluded in a heavy smoker who develops atypical pneumonitis that does not respond to conservative therapy within a few weeks' time.

In the present series of 875 cases, the lesion was so far advanced when first seen that it was considered inoperable in 330 (34 per cent) and operable in 542 (62 per cent), 20 (4 per cent) of these refusing surgery. Five hundred twenty-five (60 per cent of the entire group) were explored of whom 169 (32 per cent) were not resectable. Of these 28 (16 per cent) died within the hospital and 141 (84 per cent) left the hospital after palliative therapy with chemotherapy, irradiation or a combination of both. Three hundred fifty-six of the 525 patients explored were resected (68 per cent of those explored and 41 per cent of the total group), of whom 269 (75 per cent) had extension beyond the lung either to the mediastinal nodes, the chest wall, mediastinum, pericardium, or diaphragm. These were designated as palliative resections. Of this group 47 (17 per cent) died in the hospital, and 222 (83 per cent) left the hospital. The deaths were due principally to the extensive disease and not to the operative procedure. Of the 356 resected, the lesion was limited to the lung in 87 (25 per cent of those resected and 10 per cent of the entire group). Of this group, 9 (10 per cent) died in the hospital and 78 left the hospital. Three hundred (222 having palliative resections and 78 curative resections) left the hospital (34 per cent of the entire group of 875 cases).

As mentioned previously, it has been our belief that, whenever possible, pneumonectomy is the preferable procedure. In the present series of 356 resections, pneumonectomy was done in 94 per cent and a lobectomy in 6 per cent. The lesion had extended beyond the lung in 75 per cent at the time of resection. Of the entire group of resected cases, there was involvement of the mediastinal nodes in 60 per cent with extension limited to the nodes in 47 per cent and involvement of the pleura in 12 per cent with distant involvement in 2 per cent. Although we believe that evidence of distant involvement is a contraindication to resection, we resected these cases because we thought the lesion was limited to the lung. However, patients succumbed postoperatively, and at autopsy it was found that there were distant metastases that were not demonstrable preoperatively. In the patients with nodal involvement, the original lesion was in a lobe bronchus in 69 per cent, in a main stem bronchus in 49 per cent and in the periphery in 28 per cent.

As might be expected, lesions of main stem and lobe bronchi were associated with higher incidences of nodal metastases than peripheral lesions, and peripheral lesions were associated with higher incidences of pleural metastases. Extension from main stem bronchus lesions were nodal, 59 per cent; limited to nodes, 44 per cent; pleural, 22 per cent; and distant, 0.

These respective percentages for lobe bronchus lesions were 66 per cent; 49 per cent; 23 per cent and 5 per cent, and for peripheral lesions, 43 per cent; 25 per cent; 44 per cent and 2 per cent. Many thoracic surgeons and some pathologists believe that pulmonary resection is not indicated if there is extension beyond the lung. On the other hand we have always maintained that resection should be done if at all possible and that palliative resections are as justifiable in the treatment of pulmonary malignant lesions as palliative excisional therapy in intestinal neoplasia. If there is evidence of extension beyond the lung at the time of resection, the surgeon designates the procedure as a palliative resection, which in reality is an arbitrary clinical designation because, as will be shown subsequently, many of these patients are cured.

Following treatment of bronchogenic diseases there is a rapid decrease in the survival rate in the early postoperative period. After two years, the survival rate tends to remain stationary and is more or less the same as for the general population age. The overall survival rate in the present series was six months, 41 per cent; one year, 24 per cent; two years, 10 per cent; three years, 8 per cent; four years, 7 per cent; five years, 6.5 per cent. Twenty patients appeared to have operable lesions, but they refused surgery. Most of these patients were given some type of palliative therapy. Although their lesions appeared to be relatively early and amenable to therapy, their survival was not satisfactory as might be expected. At the end of six months, 60 per cent were alive; at the end of one year, 40 per cent; at the end of two years, 20 per cent and at the end of three years none was alive. It is thus seen that other types of therapy, such as irradiation and chemotherapy, although of real value from a palliative standpoint, are not curative. Survival rates for those patients in whom resection was done were: six months, 56 per cent; one year, 40 per cent; two years, 21 per cent; three years, 20 per cent; four years, 16 per cent; five years, 15 per cent. In the group of patients in whom the lesion had extended beyond the lung, those in whom a palliative resection was done, the survival rates were obviously not as good, because the lesion was much more extensive. However, the fact that some of them survived and are apparently well is of real significance. The survival rates in this group were: six months, 51 per cent; one year, 33 per cent; two years, 14 per cent; three years, 12 per cent; four years, 9 per cent; five years, 8 per cent. These results are significant, because some surgeons are of the opinion that once a lesion has extended beyond the lung, cure is not possible. The fact that 8 per cent of this group are alive and free from tumor at the end of five years shows that this contention is fallacious. Obviously, the survival rates were best in those cases in which the lesion apparently was limited to the lung at the time of the original operation (curative resection). In this group the survival rates were: six months, 75 per cent; one year, 64 per cent; two years, 47 per cent; three years, 44 per cent; four years, 40 per cent and five years, 37 per cent. In the group of cases in which resection was not possible either because the lesion was so far advanced at the time the patient was first seen or at the time of exploration, the survival rates were not good: six months, 29 per cent; one year, 10 per cent; two years, 1.4 per cent, and at the end of three years, one of 376 patients observed was still alive, but he died before the fourth year.

A number of factors influence survival rates, and, of course, these are important because they are of prognostic significance. As we have previously shown in our overall series, including charity and private cases, the prognosis in women is better than in men, although the disease is relatively rare in women. This is true not only in bronchogenic cancer, but also in gastric cancer. The reason for this cannot be explained at the present time. The five-year survival rate in the present series was 6.2 per cent in men and 10 per cent in women. Of the total resected cases, the percentages were 14 and 22, respectively. In the curative resections, they were 33 and 60, respectively. Only in the group of cases in which palliative resections were done, that is, in which the extension was beyond the lung, was the five-year survival rate better in men, 8 per cent and 4 per cent, respectively. However, the number of cases is so small, particularly in women, that these figures are probably insignificant. The most important prognostic factor is the extent of the lesion. By far the best results were obtained in those cases in which the lesion was apparently confined to the lung at the time of operation (curative resections). In our series, the five-year survivals in the group were as follows: less than 50, 44 per cent; 50 to 69, 34 per cent, and over 70, 33 per cent. In the group in which there was extension beyond the lung at the time of resection (palliative resection) these respective percentages were 5, 9, and 0 per cent. The five-year survival rate in all age groups with no evidence of extension at operation was 39 per cent; in those with evidence of nodal involvement but no other involvement, 14 per cent; in those with extension but no evidence of nodal involvement, 3 per cent, and those with evidence of both nodal and other involvements, 0. Another important prognostic factor is the type of lesion. Adenocarcinomas give a very poor prognosis; only 7 per cent of the present series survived five years. The five-year survival rates in the cases with epidermoid lesions was 21 per cent and in those with undifferentiated lesions, 11 per cent. Previous investigators have emphasized that lower lobe lesions offer a much worse prognosis than upper lobe lesions. A logical explanation for this is the demonstration by our associates, Dr. Kenneth Meyer,[34] of lymphatic connections between the lower pulmonary lobes and the retroperitoneal nodes. In the present series, however, this was apparently of little significance. The five-year survivals in the present series were highest in main stem lesions, 18 per cent; next in upper and middle lobes, 15 per cent, and lowest in lower lobe lesions, 13 per cent. It is evident that the results were almost identical in upper and lower lobe lesions in the present series.

When the lesions were considered according to their central or peripheral locations, the five-year survival rates were: central (main stem) 43 per cent; lobe bronchi, 37 per cent, and periphery, 36 per cent. It is thus seen that main stem lesions have a slightly better prognosis than those in other portions of the lung.

As mentioned previously, we have performed very few lobectomies for bronchogenic cancer, because we are convinced that lobectomy is not the best operation for a malignant lesion. We performed lobectomy only when careful preoperative pulmonary function studies indicated that pneumonectomy could not be tolerated. Obviously, these are poorer risk patients and, therefore, our results are not good. In the 21 cases in the present series,

66 per cent survived six months; 43 per cent, one year; 10 per cent, two years and three years, and none survived four years.

SUMMARY

Cancer of the lung is increasing more than any other cancer in both sexes and has become the most frequent cancer. Because the increased incidence is due to the almost universal use of cigarettes, it is necessary to consider its development in all heavy smokers. The diagnosis is difficult to make early.

Treatment consists of pulmonary excision, preferably pneumonectomy. Results are not good. In our series, resection was possible in only 40 per cent and there was no evidence of extension beyond the lung in only 10 per cent. Several factors, sex, extension of the lesion and the type of lesion, influence prognosis.

Because of the tremendous increase in lung cancer and the causal relationship to cigarette smoking, all smokers should have a chest x-ray film made every six months in order to diagnose symptomless pulmonary lesions before metastases occur.

RESUMEN

El cáncer del pulmón está aumentando más que cualquiera otra localización de cáncer y se ha hecho la forma más frecuente de cáncer. Puesto que el aumento de su incidencia se debe al uso casi universal de los cigarrillos, es necesario tener presente su posible desarrollo en todos los grandes fumadores.

El diagnóstico es difícil de hacerse tempranamente.

El tratamiento consiste en la excisión quirúrgica, preferiblemente la neumonectomía. En nuestra serie, la resección fué practicable sólo en 40 por ciento y no hubo evidencia de extensión afuera del pulmón en sólo 10 por ciento. El pronóstico es influído por varios factores como el sexo, extensión de la lesión, tipo de ella.

En virtud del tremendo aumento del cáncer pulmonar y la relación causal con el fumar cigarrillos, todos los fumadores deben hacerse una radiografía de tórax cada seis meses a fin de diagnosticar las lesiones pulmonares asintomáticas antes de que existan metástasis.

RESUME

Le cancer du poumon est en augmentation beaucoup plus que tout autre cancer dans les deux sexes et est devenu le cancer le plus fréquent. Parce que cette augmentation du taux est imputable à l'usage presque universel de cigarettes, il est nécessaire d'envisager la possibilité de son développement chez les gros fumeurs. La diagnostic est difficile à faire précocément. Le traitement consiste en exérèse pulmonaire la pneumonectomie de préférence. Les résultats ne sont pas bons. Dans la série des auteurs, la résection ne fut possible que chez 40% des malades et ce n'est que dans 10% des cas qu'il n'y eut pas de signe d'extension au poumon. Plusieurs facteurs, le sexe, l'extension et le type de la lésion, ont une influence sur le pronostic.

Par suite de la très grande augmentation du cancer pulmonaire et de sa relation avec la fumée de cigarette, tous les fumeurs devraient être soumis à un contrôle radiographique tous les six mois afin de permettre le diagnostic des lésions pulmonaires encore sans traduction clinique avant que les métastases ne surviennent.

ZUSAMMENFASSUNG

Der Lungenkrebs nimmt mehr als jede andere Krebsarzt bei beiden Geschlechtern zu und ist zum häufigsten Krebs geworden. Weil seine zunehmende Häufigkeit die Folge des fast universällen Zigarettenkonsums ist, muss seine Entwicklung bei allen starken Rauchern in Betracht gezogen werden. Eine frühzeitige Diagnose zu stellen, ist schwierig.

Die Behandlung besteht in einer Lungenresektion, in erster Linie der Pneumonektomie. Die Resultate sind nicht gut. Bei unserem Krankengut war die Resektion nur in 40% durchführbar und Anhaltspunkte dafür, dass der Befund nicht bereits über die Lungen hinaus reichte, lagen in nur 10% vor. Verschiedene Faktoren, wie das Geschlecht, die Ausdehnung des Befundes und der Typ des Herdes, beeinflussen die Prognose.

Wegen des gewaltigen Anstiegs des Lungenkrebses und der ursächlichen Beziehung zum Zigarettenrauchen sollten alle Raucher alle 6 Monate eine Thoraxröntgenaufnahme bekommen, um die Diagnose symptomenloser Lungenveränderungen zu stellen, ehe Metastasen auftreten.

Complete reference list will appear in reprints.

Diagnostic Pneumopericardium: Its Clinical Application

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Simple roentgenographic evaluation of the mediastinal and contiguous cardiac and pulmonary structures is frequently extremely difficult and in many instances may be impossible. The preoperative differential diagnosis of paracardiac lesions even with barium in the esophagus and after angiocardiographic techniques, has presented a problem in the past.

During the past three years we have investigated the physiological effects of the introduction of air into the intact pericardial sac in the experimental laboratory.[1] On the basis of information obtained from these experiments a simple safe technique for the introduction of air into the pericardial space for diagnostic purposes has been evolved and applied in a series of patients.

Review of Literature

Historically, little interest has been focused upon pneumopericardium in the past. Practically all case reports have concerned traumatic or spontaneous varieties of pneumopericardium[2, 3] (radium necrosis, erosion by ulcer or carcinoma of the esophagus and stomach). In a review of the literature we have encountered only four reports, all by the same authors, on elective penumopericardium as a diagnostic procedure.[4-7] This paucity of information most probably results from the generally prevalent impression among physicians that air in the pericardiac space is a highly dangerous if not fatal occurrence because of possible tamponade and heart standstill. As late as 1930 and 1932, Beck, Cox, and Isaacs[8, 9] reported on the adverse tamponade effects of simply exposing the heart to atmospheric pressure and suggested that some of the late deaths following thoracotomy and pericardiotomy resulted from this adverse effect.

Anatomical and Physiological Considerations

Some factual information does exist regarding the anatomy and physiological functions of the pericardium.

Anatomically, the pericardium is a fibro-serous sac in which the heart and roots of the great vessels are contained. The serous layer of the pericardium is continuous with the epicardium at the junction of the pericardium and the great vessels as they come out of the heart. The epicardium covers the heart and great vessels. The enclosed sac or the pericardial cavity is merely a potential space. It has been amply demonstrated that the potential volume of the pericardial space, however, is much larger than that occupied by the normal heart in diastole. Circumstances have been encountered, however, in which the pericardium does definitely influence the heart size and the cardiovascular dynamics. The degree to which this influence can be exerted would depend upon the distensibility of the peri-

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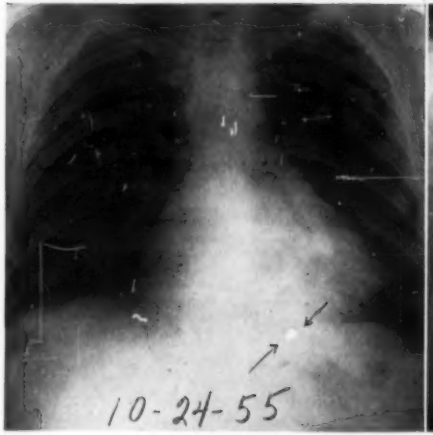

FIGURE 1

FIGURE 2

FIGURE 3

Figure 1 (Case 2): Plain roentgenogram of chest does not permit accurate localization of shell fragment in pericardium, heart or diaphragm.—*Figure 2* (Case 2): Roentgenogram of chest with air in stomach shows shell fragment is not in left diaphragm.—*Figure 3* (Case 2): Diagnostic pneumopericardium accurately localizes foreign body in the heart.

cardium per se. This in turn, according to some investigators, is directly related to the structural composition of the pericardium; namely, the interwoven pattern of elastic fibers and the less distensible collagen fibers. Distention of the pericardium is accompanied by stretching of the elastic fibers. After these are stretched to their maximum, further dilation is hindered by the collagenous fibers.

An excellent report on the role of the pericardium in the regulation of cardiovascular hemodynamics was presented by Berglund and his associates in 1955.[10] Their experience with animals resulted in the observations that the pericardium restrains diastolic expansion and therefore ventricular work at high atrial or end-diastolic ventricular pressures. They also reported that the pericardium limits the elevation of pulmonary capillary pressure when the left ventricle is placed under stress. This is accomplished because the pericardium restrains diastolic expansion of the right ventricle and therefore limits right ventricular work. The consequences are lower pulmonary capillary and left atrial pressures than would ordinarily result if the pericardium were not present. The pericardium protects against tricuspid or mitral valve regurgitation at high ventricular filling pressures.

Animal Experiments

Experimental physiological studies carried out in a series of dogs[1] have indicated that the effect of the introduction of air into the intact pericardium is directly related to the intrapericardial pressure at any given moment. Cardiac output ceases at an established critical pressure. Detailed investigations utilizing strain-gauge measurements of inflow and outflow pressures correlated with electrocardiographic tracings were recorded during the introduction of known quantities of air under measured pressures into the intact pericardial sac.

Procedure

Mongrel dogs weighing 12-15 kg. were used in the experiments. The procedures were completed through the open chest under I.V. nembutal. A catheter was inserted by way of the right jugular vein into the right auricle. A second catheter was inserted by way of the right carotid artery into the aorta. With these arrangements inflow and outflow pressures could be obtained. A needle with a specially devised plastic flange was used for leakproof delivery of air into the pericardial sac. A known quantity of air at known pressure was then injected into the pericardial sac.

Results

1. An average pressure of 16-20 cm. of water produced prompt fall in the outflow tract (arterial) pressure. Before this occurred the inflow tract (venous) pressure rose slowly. An average of 200-250 cc. of air was necessary to produce these changes.

2. The rate of instillation of air was an important factor in the production of fall of the atrial pressure and elevation of the venous pressure. Air instilled rapidly occasionally produced a precipitous change, whereas if several minutes were used for the instillation, the pressure changes were delayed or did not occur at all.

3. An interesting finding in the dog with a catheter in the left auricle

was that the left auricular pressure changed very little if any regardless of the amount of air instilled or the intrapericardial pressure at any given moment.

Technique—Diagnostic Pneumopericardium in Patients

On the basis of information obtained from animal experiments, a simple, safe, technique for the introduction of air into the pericardial sac was evolved and applied in a series of patients. The technique is as follows:

1. With the patient supine and utilizing local anesthesia the third left intercostal space, 1½ to 2 cm. to the left of the border of the sternum is localized. A No. 20 or 22 gauge lumbar puncture needle with the stylet in place is inserted slowly. Using tactile sensation as a guide the needle point is advanced directly through the anterior intercostal membrane at which point a feeling of "give" will be experienced. From this point on the needle is advanced slowly and gently until a solid structure, the heart, is encountered. The needle will move synchronously with the heart beat. It should immediately be withdrawn approximately one to three mms. and at this point should rest in the intrapericardial space. Occasionally scratching sensations will be palpable at the tip of the needle. This is merely another indication that the needle tip is in the proper location.

2. A hemostat is placed about the needle at skin level so that it does not advance beyond this point and the apparatus is connected to either a pneumothorax machine or a syringe with three-way stopcock.

3. One hundred ccs. of air is slowly injected and pressure records are maintained. Depending upon the size of the patient 100 to 500 ccs. of air should be instilled. The rate of injection should be appreciably reduced after the instillation of the first 100 cc. of air to allow the heart to adjust to the increasing pressure change.

4. The needle is removed and the patient is postured so that the air will

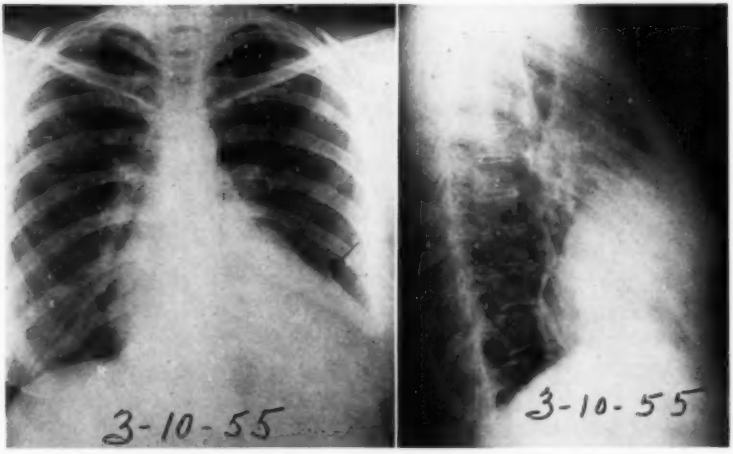

FIGURE 4A FIGURE 4B

Figure 4A and *4B* (Case 4): P. A. and lateral roentgenograms chest demonstrate an enlarged cardiac silhouette.

rise on the particular side to be investigated. For example, the patient should be postured on the right side if films are to be made of the left cardiac border in the lateral prone position. An upright position is necessary if visualization of the upper part of the pericardial cavity is to be obtained.

5. Fluoroscopic examination has been of little help in evaluating the presence or absence of an adequate pneumopericardium.

Case Reports

Case 1: L. M. White Man, age 18 years. One year prior to admission to the hospital this patient sustained an injury to the left anterior chest when a jack gave way while he was under a car. Roentgenograms of the chest showed a foreign body in the vicinity of the heart. However, the exact location was not accurately determined. Following the accident he experienced increasing easy fatigability and was diagnosed as having a questionable disorder of the heart. He was admitted to the hospital where fluoroscopy and roentgenographic examination of the chest showed the heart enlarged and globular. The venous pressure was moderately elevated and the circulation time was prolonged. There was no ascites or peripheral edema. The heart sounds were somewhat muffled, but otherwise presented no murmurs or arrhythmias. Critical evaluation of the activity of the cardiac chambers was impossible by fluoroscopy. Accordingly, on May 28, 1956 a needle was inserted into the pericardial sac. No fluid was obtained. Approximately 300 cc. of air was instilled into the pericardial cavity, following which roentgenograms were obtained. This examination showed marked thickening of the parietal pericardium, but more importantly, for the first time fluoroscopic examination and critical evaluation of the motion of the cardiac chambers was possible. Following distention of the pericardial sac it was possible to accurately demonstrate that there was very *marked* limitation of activity of the chambers indicating a constrictive pericarditis. He left the hospital and was prepared for subsequent operation which was performed on September 25, 1956. At this time a complete pericardiectomy was performed through a median sternotomy incision. At operation the pericardial cavity contained old fibrinous deposits heavily stained with hemoglobin pigment. The pericardium which was thickened as previously demonstrated by pneumopericardium was completely excised around to the phrenic nerves. The foreign body was not palpable in the heart and no attempt was made to remove it. There was a dense deposit of thick scar tissue over the epicardium completely limiting the activity of all chambers of the heart particularly marked over the left and right ventricular chambers. Complete decortication of the heart was easily accomplished following which there were excellent pulsations of all chambers. The postoperative course was satisfactory and the result has been excellent. The clinical diagnosis was traumatic hemopericardium resulting in constrictive pericarditis.

Comment: Diagnostic pneumopericardium was of distinct value in the preoperative evaluation and establishment of a final diagnosis in the in-

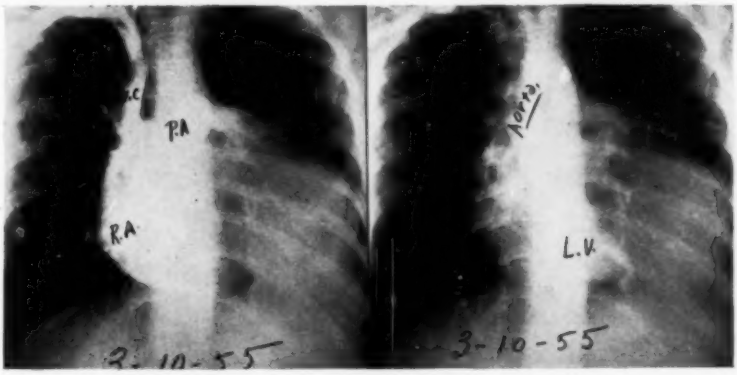

FIGURE 5A FIGURE 5B

Figure 5A and *5B* (Case 4): Angiocardiogram—inflow and outflow tracts suggests but is not conclusive that an extracardiac mass is present on the left.

stance of this patient who presented inconclusive clinical findings suggesting constrictive pericarditis.

Case 2: E. B. This 31 year old white man was admitted to the hospital October 16, 1955 complaining of intermittent, constantly recurring, dull, occasionally sharp pain over the left anterior chest and increasing dyspnea. He had sustained a shrapnel injury of the left chest in the Korean Conflict. A plain roentgenogram of the chest October 24, 1955 showed questionable enlargement of the cardiac silhouette and the presence of a metallic fragment which could not be accurately localized in the pericardium, heart or diaphragm (Fig. 1). Repeat x-ray films of the chest on October 27, 1955 following the instillation of air into the stomach by nasal catheter demonstrated that the foreign body was not in the diaphragm (Fig. 2). Its location, however, relative to the pericardium and heart was still unsettled. Diagnostic pericardicentesis October 28, 1955 yielded only 10 cc. of serosanguineous fluid. Following the instillation of 250 cc. of air and repeat x-ray films of the chest, the foreign body was accurately localized in the myocardium (Fig. 3). *Operation* November 3, 1955: An irregular piece of shell fragment 2 cm. in diameter was successfully removed from the heart. Postoperatively he did well and is completely relieved of his symptoms.

Comment: Diagnostic pneumopericardium in this patient permitted accurate preoperative localization of a metallic foreign body in the heart. Conventional diagnostic procedures were of no help. Accurate localization made possible a more direct approach to the shell fragment.

Case 3: R. W. This 50 year old white woman was seen in consultation on July 18, 1956 because of the incidental x-ray film finding of a left paracardiac density. She had no symptom whatsoever referable to her chest. Bronchoscopic examination showed entirely normal findings. No pulsation was noted in the mass by fluoroscopic examination. Carcinoma of the lung was suspected despite the absence of pulmonary symptoms. To more accurately determine the anatomical origin of the lesion and its possible relationship with the pericardium, diagnostic pneumopericardium was carried out on July 24, 1956 when 150 cc. of air was instilled into the pericardial cavity. Posterioanterior and lateral projection roentgenograms were obtained. These pictures showed a mass which was definitely extracardiac and suggested that the lesion might be an operable one. Thoracotomy July 7, 1956 established the diagnosis of a primary car-

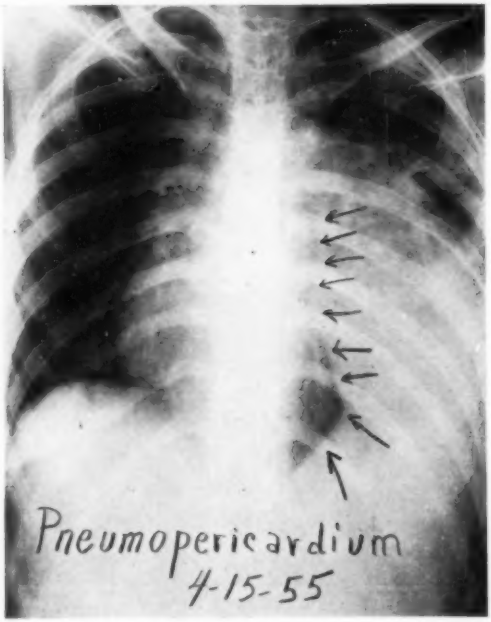

FIGURE 6 (Case 4): Pneumopericardium definitely demonstrates mass in outside of pericardium.

cinoma of the lung without invasion of the vessels as they pass through the pericardium. Unfortunately, the carcinoma extended high on the trachea beyond a point where resection was feasible, and the case had to be considered an inoperable one.

Comment: Diagnostic pneumopericardium in this patient was of real value in demonstrating that a paracardiac density was actually extracardiac and obviated specialized cardiovascular studies such as an angiocardiogram.

Case 4: J. W. This 35 year old white woman was first seen on February 22, 1955 because of dyspnea and occasional intermittent dull pain over the left anterior chest. Fluoroscopy by the referring physician showed a paracardiac density on the left. There was a past history of intermittent murmur over the left border of the heart, the exact phase of which had been undetermined. Posterio-anterior and lateral projection roentgenograms of the chest March 10, 1955 demonstrated a cardiac silhouette which suggested enlargement of the heart, pericardial effusion or a contiguous para-

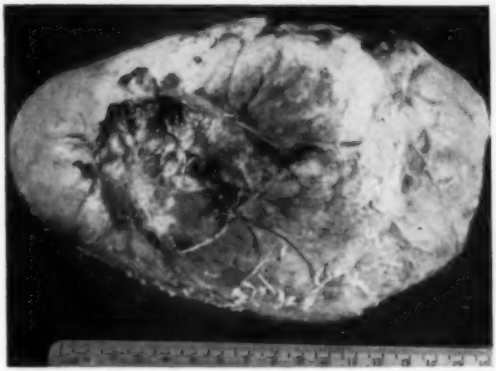

FIGURE 7 (Case 4): Photograph of pericardial fibroma removed at operation.

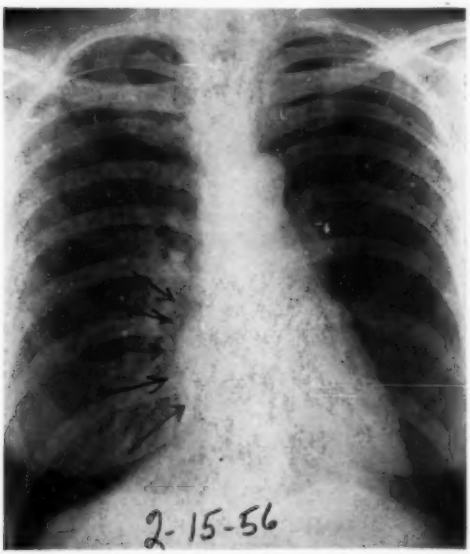

FIGURE 8 (Case 6): P. A. roentgenogram chest shows paramediastinal density thought to be tumor.

cardiac tumor (Fig. 4A and 4B). An angiocardiogram performed the same day suggested that the mass was not cardiac in origin, but was not definitely conclusive (Fig. 5A and 5B). Diagnostic pneumopericardium April 15, 1955 demonstrated without reservation that the mass was outside of the pericardium (Fig. 6). Operation the same day revealed a large tumor 16 x 11 x 7 cm. in diameter and weighing 630 grams situated in the anterior lower mediastinum and intimately adherent to the pericardium. The lesion was completely removed and on microscopic section was demonstrated to be a benign fibroma (Fig. 7). The postoperative convalescence has been uneventful.

Comment: In this particular patient the angiocardiogram failed to give accurate information regarding the point of origin of the lesion. This was

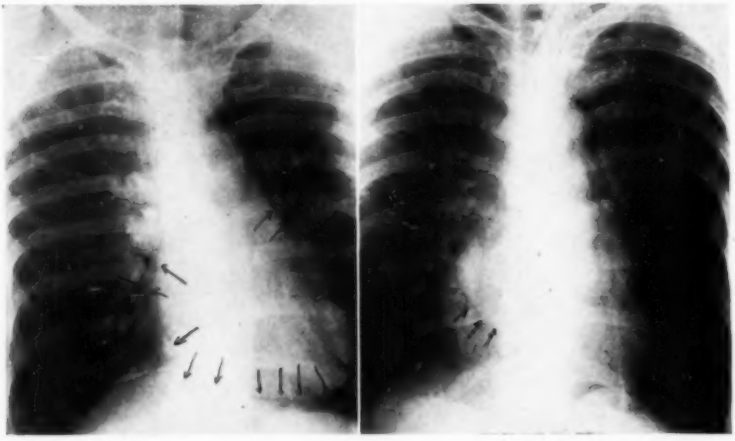

FIGURE 9A FIGURE 9B

Figure 9A and *9B* (Case 6): Diagnostic pneumopericardium shows the mass to be entirely inside the pericardium probably cardiac in origin.

FIGURE 10 (Case 6): Angiocardiogram demonstrates that density protruding to rt. of midline is really an enlarged lt. auricle. Hold up of dye in the lt. auricle and slow filling of the lt. ventricle suggested the diagnosis of mitral stenosis.

finally determined by preoperative diagnostic pneumopericardium.

Case 5: J. Y. This 50 year old white man was admitted to the hospital because of an asymptomatic mass which was retrocardiac in location. Extensive investigation including fluoroscopy and various projection roentgenograms of the chest did not help in determining the origin or etiological background of the mass. Barium esophagogram did exclude the possibility of origin from the esophagus or the upper end of the stomach. In the differential diagnosis aneurysm of the aorta, pericardial celomic cyst, and primary tumor of the lung were considered. Diagnostic pneumopericardium was performed on November 14, 1956 at which time 300 cc. of air were instilled. This examination clearly showed that the mass was extracardiac in location and probably mediastinal in origin. Exploration of the chest on December 13, 1956 showed a large mediastinal cyst which was intimately adherent to the aorta and esophagus. This was completely removed without event.

Comment: Preoperative diagnostic pneumopericardium in this patient excluded the possibility of aneurysm of the aorta and the possibility of pericardial or cardiac origin of the mass.

Case 6: L. H. This 50 year old white woman was first examined on January 31, 1956 because of shortness of breath of four months duration and a hacking, unproductive cough that had been present for many years. Roentgenogram of the chest on February 15, 1956 revealed a paramediastinal mass on the right which was impossible to separate from the cardiac silhouette. The diagnosis of mediastinal tumor was entertained (Fig. 8). Bronchoscopic examination showed normal findings. An intermittently present murmur was audible over the precordium, but the exact phase could not be determined. Because of the intermittent murmur, the history of dyspnea and difficulty encountered in evaluating fluoroscopically the density in the right paramediastinum, diagnostic pneumopericardium was carried out on February 16, 1956, when 300 cc. of air were instilled. This examination demonstrated that the mass was entirely within the pericardium, probably cardiac in origin (Fig. 9A and 9B). Thoracotomy was cancelled until additional studies could be completed. Angiocardiogram on February 23, 1956 established the fact that the density seen to the right of the midline was in reality an enlarged left auricle (Fig. 10). There was definite hold-up of the dye in the left auricle and slow filling of the ventricle. These findings, along with the history of recent dyspnea and murmur, suggested that we were dealing with mitral stenosis with an enlarged left auricle that protruded to the right of the midline. Commissurotomy has been suggested, but has not been accepted.

Comment: Preoperative diagnostic pneumopericardium in the instance of this patient obviated unnecessary exploratory thoracotomy to establish a definite diagnosis of intrinsic heart disease.

SUMMARY AND CONCLUSIONS

1. Diagnostic pneumopericardium has been an overlooked diagnostic "tool" that can give valuable preoperative information regarding the precise origin of paracardiac, cardiac, pericardial and contiguous diaphragmatic lesions.

2. The preoperative information obtained by diagnostic pneumopericardium permits a direct, accurate, and less time consuming surgical approach to lesions in and about the heart, pericardium and mediastinum.

RESUMEN

1. El neumopericardio diagnóstico es un método desdeñado que puede dar valiosa información preoperatoria respecto del origen preciso de lesiones paracardiacas, cardiacas, pericárdicas, y de lesiones diafragmáticas contíguas.

2. La información preoperatoria obtenida por el neumoperitoneo diagnóstico permite una táctica directa, exacta y más corta en la cirugía del corazón, del pericardio y del mediastino.

RESUME

1. Le pneumopéricarde institué dans un but de diagnostic est un moyen qui a été négligé. Il peut donner des informations préopératoires valables, en ce qui concerne l'origine précise des lésions paracardiaques, cardiaques, péricardiques et contiguës au diaphragme.

2. Les renseignements préopératoires obtenus par ce moyen diagnostique permettent une approche chirurgicale directe, précise et rapide des lésions avoisinant ou atteignant le coeur, le péricarde et le médiastin.

ZUSAMMENFASSUNG

1. Das diagnostische Pneumoperikard war ein vernachlässigtes diagnostisches "Werkzeug," das wertvolle präoperative Information liefern kann hinsichtlich des genauen Sitzes von paracardialen, cardialen, pericardialen und benachbarten Zwerchfell-Herden.

2. Die präoperative Information, die man mit dem diagnostischen Pneumopericard gewinnt, gestattet einen direkten, akkuraten und weniger zeitraubenden chirurgischen Zugang zu Befunden in und um das Herz, Perikard und Mediastinum.

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Epidemiological Aspects of Tuberculosis in Brazil*

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Based on information resulting from surveys and investigations as well as statistical data relating to infectiousness, mortality and morbidity, the Epidemiology Section of the National Tuberculosis Service has been trying, since 1946, to exercise its activities with a view to providing permanent knowledge regarding tuberculosis epidemiology in Brazil and to follow up the progress of the struggle against this disease throughout the country.

With this aim it has maintained close contact with the Federal Biostatistics Service and with State Public Health offices, from which it has been receiving all possible collaboration in the form of periodic remittance of data in connection with vital facts which have occurred and which bear on its studies and researches.

The Epidemiology Section has likewise promoted tuberculin and x-ray film surveys and contributed to the setting up and operation of both mobile and permanent x-ray film centers in several regions of Brazil.

Such surveys and the coordination of research in these areas have resulted in greater knowledge with regard to the problem of tuberculosis, some of the information obtained having already been published in a series of studies prepared by members of the National Tuberculosis Service and by other experts to whom the existing data were made available.

It should be noted that the first researches with a view to establishing the bases of the "National Anti-Tuberculosis Campaign" were carried out in collaboration with the experts of this Section which, gradually and within its possibilities, has been expanding and developing its activities.

In this study we present some statistics, and based on these data take the opportunity of giving a brief explanation of facts observed during the period 1946-1955.

In the interpretation and analysis of the data we shall now discuss, it should be borne in mind that some are faulty due to deficient notification of cases and even, in certain areas, to difficulty in obtaining a complete record of vital facts, especially those relating to morbidity.

It is true that such inaccuracies occur throughout the period under consideration; there are signs that they have improved with the course of years, and the trend of events leads us to accept the data available as capable of representing reality. It should be remembered, however, that if the much more reliable data referring to mortality rate still call for a certain reserve, morbidity rate statistics—insofar as incidence and especially prevalence are concerned—besides those questionable ones relative to case-fatality-rate and infectiousness are far from giving a truly accurate picture.

Mortality

In 1946, when the National Anti-Tuberculosis Campaign was instituted,

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the disease represented one of the most serious public health problems in the country, decimating the most productive sector of the population of large demographic groups.

In that year the mortality rate for all the Brazilian State capitals including Rio de Janeiro, D.F. reached 246.0 per 100,000, with some towns or counties, as for instance Vitória, registering 498.7, Terezina 399.0, Salvador 397.0, Porto Alegre 356.0 and Recife 335.0. In none of these capitals was the ratio lower than 100.0. Mortality in the age group between 20 and 39 often reached over 400 deaths per 100,000 inhabitants, and in the majority of cases tuberculosis appeared as the chief "causa mortis."

After 10 years the problem of tuberculosis, on the basis of mortality data, presented a marked change. During the year 1954 in none of the Brazilian State capitals was the mortality rate above 200.0, having dropped in eight of them below 100, and in four to less than 50 deaths per 100,000 inhabitants.

Average mortality for all capitals fell from 245.6 in 1946 to 84.8 in 1954 (Table I), representing a decrease of 65.5 per cent which corresponds to the survival of 57.866 people who would have died, had the mortality rate prevailing in 1946 been maintained in the succeeding years. In addition to this, in the majority of these towns or counties tuberculosis is no longer first place among the various causes of death.

Mortality, however, continued still higher in Vitória, with 182.0, there following in decreasing order Terezina, Salvador, Belém, Porto Alegre, Maceió, Fortaleza and Belo Horizonte, with over 110.0. The remaining capitals and Rio de Janeiro, D.F. showed lower death rates, the lowest of all being registered in São Paulo, with 36.0 per 100,000 inhabitants.

Age and Sex

Age: In Rio de Janeiro, D.F. mortality in the age-groups 20 to 39 fell from 431.1 in 1946 to 111.9 in 1954, i.e., a decrease of 75.0 per cent, it being noted that death from tuberculosis, though markedly reduced in all age-groups, seems to have shifted from the younger to the older groups.

TABLE I

BRAZIL*

ANNUAL NUMBER OF DEATHS AND MORTALITY RATES PER 100,000 INHABITANTS OVER THE PERIOD 1946-1955

Years	No. of Deaths	Mortality Rates	Percentage Variation
1946	17,135	245.6	—
1947	17,300	238.8	— 2.8
1948	16,540	220.2	— 7.8
1949	14,909	191.7	—13.0
1950	14,075	175.1	— 8.7
1951	14,133	170.0	— 2.9
1952	10,809	125.9	—26.0
1953	7,577	85.7	—31.9
1954	7,729	84.8	— 1.1
1955**	6,414	99.4	+14.7

*Data referring to all State capitals and Rio de Janeiro, D.F.
**Not including Manaus, João Pessôa and São Paulo.

In 1955 Rio de Janeiro, D.F. presented, for instance, in the age-group 20 to 29 the mortality rate of 91.1, while in the age-groups 40 to 49 and 50 to 59 it reached respectively 147.8 and 171.2 (Table II).

The percentual variation of specific rates does permit us to state that the decline did not make itself felt with the same intensity in all stages of life. The reduction was more pronounced in the groups 10 to 14, 15 to 19, 20 to 29 and 30 to 39 years, where differences were observed which varied from 70.8 to 90.5 per cent as for instance in the case of the 15 to 19 age-group.

The mortality rate observed in the older groups may, however, represent the accumulation of deaths resulting from prolonging patients' lives, rather than an actual increase.

Sex: As far back as 1946 mortality rate from tuberculosis in Rio de Janeiro, D.F., taking into consideration all age-groups, was higher among men (337.6) than among women (249.3). There was a difference of 25.8 per cent between the two groups. It is important to note, however, that in 1950 this difference rose to 32.2, reaching 45.6 in 1955 (Table III).

During the period 1946-1955 there was, undoubtedly, a remarkable decline of mortality in both groups. While among men, however, the total decrease was from 339.0 per 100,000 to 116.3, i.e., 65.5 per cent in the women group it reached 74.6, falling from 249.3 to 63.3, thus revealing greater difference among the rates for men (-221.3) than for women (-186.0), notwithstanding a much greater relative decrease in the latter group.

The interesting point, however, is that the decrease of mortality in both sexes was more marked precisely in the age-groups 10 to 14 and 15 to 19, with 88.8 and 90.5 per cent respectively, while the group 10 to 14 was the one which, in 1955, showed the lowest mortality rate, with only 6.2 per 100,000 inhabitants (Table II). These facts would seem to indicate the need for revising the concepts put forth in connection with a possible "un-

TABLE II

RIO DE JANEIRO, D.F.

MORTALITY FROM TUBERCULOSIS (ALL FORMS) BY AGE-GROUPS WITH PERCENTUAL VARIATION IN THE PERIOD 1946-1955

(RATE PER 100,000 INHABITANTS)

Age (Years)	1946			1955			Percentage Variation 1946-1955
	Population	Number of Deaths	Rates Per 100,000	Population	Number of Deaths	Rates per 100,000	
0- 4	228,273	247	108.3	296,412	156	52.6	—51.4
5- 9	193,658	76	39.2	221,918	35	15.8	—59.7
10-14	196,770	109	55.4	224,328	14	6.2	—88.8
15-19	214,666	648	301.9	275,164	79	28.7	—90.5
20-29	444,368	1,886	424.4	574,202	523	91.1	—78.5
30-39	337,627	1,485	439.8	414,622	531	128.1	—70.8
40-49	242,713	967	398.4	311,815	461	147.8	—62.9
50-59	131,144	533	352.6	196,783	337	171.2	—51.5
60+	116,391	272	233.7	181,401	269	147.7	—36.8

favorable interference" of the internal secretory activity of puberty on mortality from tuberculosis.

It should be pointed out that the percentuals of reduction to which we have referred generally indicate the relative importance of occurring variations as compared with corresponding initial levels. They do not indicate the importance of the absolute variation observed in the number of deaths with relation to population, which, incidentally, was quite marked.

As we have already had occasion to comment while comparing mortality rates by sex in Rio de Janeiro, D.F., smaller variations are sometimes encountered which are, however, of greater relative importance.

Justification of the Decline

Mortality from tuberculosis has been declining in Brazil since the beginning of the century. This decline, however, was more or less slow. Several factors were indicated as being responsible for the reduction then observed, including the improvement of socio-economic conditions, natural selection, the progressive increase of the resistance of populations to the aggressive forces of the Koch bacillus—result of the struggle put up by man for his own survival.

The sharp, rapid and even unexpected decline observed during the last decade, however, and especially during the last years, coincided precisely with the recent progresses of medicine and sanitary organization, that is to say, with the setting up and operation of the National Anti-Tuberculosis Campaign, the utilization in an ever increasing proportion of means of eluding the disease, and the extraordinary action of new chemotherapeutics.

In the period 1945-1949, for instance, which presented little income from the application of the new therapeutic agents, when isoniazid was not yet being used, the ratio of reduction of the average rate of mortality in the Brazilian capitals did not go beyond 26.3 per cent, whereas in the period 1950-1954, when it became possible to utilize the profilatic and therapeutical resources available in larger scale the reduction attained 51.6 per cent. The percentual variation registered from year to year was more

TABLE III

RIO DE JANEIRO, D.F.

COMPARISON OF TUBERCULOSIS MORTALITY RATES (ALL FORMS) BY SEX AND AGE 1946-1955

Age (Years)	Mortality Rates Per 100,000				Percentage Variation 1946-1955	
	Males		Females			
	1946	1955	1946	1955	Males	Females
0- 4	108.5	54.0	107.9	51.2	50.2	52.5
5- 9	40.2	15.3	38.3	16.2	62.0	57.7
10-14	33.5	4.6	76.0	7.7	86.3	89.9
15-19	265.6	25.9	334.9	31.3	90.2	90.7
20-29	412.1	94.3	436.6	87.9	77.1	79.9
30-39	516.4	182.8	361.8	76.7	64.6	78.8
40-49	549.8	216.6	241.6	84.0	60.6	65.2
50-59	533.9	256.5	179.7	92.1	52.0	48.7
60+	424.3	223.5	104.0	78.9	47.3	24.6
All Ages	337.6	116.3	249.3	63.3	65.6	74.6

pronounced between 1951 and 1952, and between 1952 and 1953, with 26.0 and 31.9 per cent respectively (Table I).

On the other hand, the percentage of decrease of mortality rates in several countries, including Brazil, in the period 1947-1953, for instance, was quite similar, notwithstanding epidemiologic and socio-economic conditions often varying from one to the other.

Thus, despite showing different epidemiological structure, Brazil, Chile, the United States and England, Australia and Japan, for instance, show a reduction of approximately 64 per cent (Table IV).

If we now consider that during the past years the progresses made in the field of hygiene and sanitary organization have been counteracted by socio-economic disturbances, the national policy of monetary and bureaucratic inflation—factors which are capable of hampering the standard of living of the greatest part of the population and precisely that on which tuberculosis shows greatest incidence—we shall be led to believe that the recent stress on the fall of mortality resulted really from the application of chemotherapeutics, of what has been customary to call "direct fight against tuberculosis."

Present Situation

The situation has improved considerably. In every State capital, with the exception of Goiânia (28.6 per cent), the fall of mortality went beyond 50. It should be pointed out, however, that in 1954, as compared with the preceding year, the general reduction observed was only 1.1, a slight increase in mortality rates from tuberculosis being noticed in 10 Brazilian capitals; in 1955 this increase already included 11 of the 18 cities for which data are available up to now.

TABLE IV

MORTALITY FROM TUBERCULOSIS IN VARIOUS COUNTRIES
PERCENTUAL VARIATION FROM 1947 TO 1953
(RATES PER 100,000 INHABITANTS)

Countries	1947	1953	Percentual Variation 1947-1953
Brazil*	239	86	—64
Uruguay	99	40	—60
Argentina	72	40	—44
Chile	255	82	—64
United States	33	12	—64
Canada	42	12	—71
Mexico	50	31	—38
Puerto Rico	192	47	—76
England and Wales	55	20	—64
Denmark	30	10	—67
Portugal	155	63	—59
France	79	37	—53
Ceylon	56	30	—46
Australia	30	11	—63
New Zealand	31	12	—61
Japan	188	66	—65

*Data relating to the 20 State capitals and Rio de Janeiro, D.F.

In addition to this, in none of the capitals where mortality continued to fall—with the exception of Recife—did this decline, in comparsion with the preceding year, show percentage variations as high as in 1952 and 1953.

It is interesting to note, further, that whereas in Vitória mortality increased between 1953 and 1955 by 32.6, in Recife it fell 33.7. This latter city, which in 1946 appeared among the capitals whose mortality rates from tuberculosis were the highest, in 1955 began to appear among those of lowest mortality, ranking below Rio de Janeiro, D.F., with 81.0 per 100,000 inhabitants.

Thus, mortality from tuberculosis in the largest demographic centers of the country, whose decline was general and remarkable, has in the last two years been behaving in a manner different and peculiar to each one, now seeming to become stabilized, now increasing, now continuing gradually to decrease.

The causes for these phenomena—also of sudden occurrence, since as recently as 1953 the decline, as we have seen, reached 32 per cent a percentage never attained from one year to the other—are being the object of studies. The period of observation is short to permit a precise evaluation of possible causes, although some researchers believe that the number of deaths is being increased now at the expense of surviving "chronic", "incurable" patients, and also due to the emigration of patients from the interior to the capitals in quest of therapeutic resources, which would be, in this case, a loaned mortality.

It cannot but cause certain apprehension, however, to realize that, in addition to the facts already referred to, in 1953 the average mortality rates from tuberculosis in 18 Brazilian capitals reached 99.4 per 100,000 inhabitants, a figure which may represent a variation of 14.7 per cent more should the addition of the data from São Paulo, João Pessôa, and Manaus, as it appears, not determine substantial modifications (Table II).

Morbidity

The knowledge of morbidity is, especially nowadays, of great importance in the organization of programs to combat tuberculosis.

Thus, although the data available may, as we have already stressed be imperfect and as get unsuitable for evaluation, as in the case of those relating to mortality, we herein make an attempt towards better elucidation of the question.

The "abreugrafia," which is being increasingly utilized, has permitted the detection of a greater number of cases and thus contributed to the improvement of statistics.

It is true that, despite the progress achieved, only a percentage of cases have been found in its initial form, which has determined the inclusion as "new cases" of persons who contracted the disease at an earlier period. Among the 98,825 patients registered at dispensaries, for instance, in the 1948-1955, 71,085, (72.0 per cent) had moderately advanced (38.0) or very advanced (34.0) forms at the time of registration. These knowledge of "cures" should not constitute a reason for giving up the endeavors to find out facts of increasing importance to the anti-tuberculosis fight.

Incidence

Data utilized for the knowledge of incidence were obtained in publica-

tions of the Federal Service of Biostatistics and supplemented by those furnished by the States and are, naturally, subject to alterations.

A study of these data, however, reveals that the number of new cases registered in the Brazilian capitals fell from 22,153 in 1946 to 15,659 in 1954. The rate per 100,00 inhabitants thus fell from 317.5 to 171.9 (Table V), i.e., –145.6, with a percentage variation of –46.9 per cent; a variation more or less equal to that verified in Germany between 1947 and 1953, for instance, with –45 per cent, in Northern Ireland, with –43, Iceland, with –49 and Sweden, with –47; and greater than that verified in the United States, Canada and France, with –29, –33 and –16 respectively, as well as in other countries (Table VI).

Morbidity rates, however, have fallen less than those of mortality, i.e., the number of new cases has not decreased in the same proportion as the number of deaths.

The situation appears, nevertheless, to have improved. But, here also, it would be well to emphasize that the year to year percentual variation in the period 1946-1954 which, with the exception of slight fluctuations, presented reductions, of about 21 and 25 per cent between 1953 and 1954 showed an increase of 11.8, this increase coinciding with the lower percentual of decrease verified in mortality, –1.1 throughout the period under consideration.

Prevalence

For many years, owing to the well-known difficulties in obtaining other data, prevalence estimates were made solely on the basis of number of deaths, a method which would lead to even more serious errors.

Drolet and Lowell, on the premise that the total number of tuberculosis cases existing in a given period (new as well as old cases) represented

TABLE V

BRAZIL*

MORTALITY AND MORBIDITY (INCIDENCE AND PREVALENCE) OF TUBERCULOSIS IN THE BRAZILIAN CAPITALS, INCLUDING RIO DE JANEIRO, D.F. 1946-1954 (RATES PER 100,000 INHABITANTS)

		Mortality		Morbidity			
				Incidence		Prevalence	
Years	Population	No. of Deaths	Mort. Rates	New Cases	Rates	Exist. Cases	Rates
1946	6,977,765	17,135	245.6	22,153	317.5	8,610	123.4
1947	7,244,367	17,300	238.8	21,341	294.6	12,651	174.6
1948	7,510,969	16,540	220.2	21,698	288.9	17,809	237.1
1949	7,777,571	14,909	191.7	21,264	273.4	24,164	310.7
1950	8,044,173	14,075	175.0	17,364	215.8	27,453	341.3
1951	8,310,775	14,133	170.0	18,535	223.0	31,855	383.3
1952	8,577,377	10,803	125.9	14,351	167.3	35,397	412.7
1953	8,843,979	7,577	85.7	13,416	151.7	41,236	466.3
1954	9,110,581	7,729	84.8	15,659	171.9	49,166	539.6

*Data relating to the 20 State capitals and Rio de Janeiro, D.F.

three or four times the number of new cases observed in the same period, recently estimated that the number of sick persons existing in the United States would have reached a figure between 350,000 and 400,000.

If we were to consider this estimate as satisfactory; we would verify that the number of "existing cases" in the Brazilian capitals and Rio de Janeiro, D.F. would lie between 37,000 and 63,000 in 1954.

In the estimate of prevalence, however, it is more correct, although not always possible, to use the formula:

$$P = \frac{(NC + OC - (TD + PC)}{\text{Population}}$$

Where: NC = new cases detected during the year;
OC = cases brought forward from the previous year (surviving at 31st December);
TD = total number of deaths occurring during the year;
PC = number of patients cured during the year.

Applying the known values, we verify that in the period 1946-1954 the prevalence of tuberculosis in the Brazilian capitals and Rio de Janeiro, D.F., did not follow mortality and incidence, but showed itself to be in absolute ascension. While in 1946 the number of "existing patients" December 31 reached 8,610, in 1954 it was 48,945.

If we apply these numbers to the population, it will be seen that the rate per 100,000 inhabitants rose from 123.4 to 537.2 i.e., a variation of over 77.0 (Table V).

It should be pointed out that the data relating to cures, in view of their being extremely precarious, were not utilized in the calculation. However, although it may be argued that the smaller the number of deaths the greater the number of cures, as far as tuberculosis is concerned this is not exactly what has been happening. The number of deaths has been reduced much more at the expense of the prolongation of survival than due to actual cures. And even these, to take place, have required individ-

TABLE VI

MORBIDITY RATES (INCIDENCE) PER 100,000 POPULATION IN SEVERAL COUNTRIES, WITH PERCENTUAL VARIATIONS, BETWEEN 1947 AND 1953

Countries	1947	1953	Rate Variation	Percentual Variation
Brazil	295	151	—144	—49
Germany	400	219	—181	—45
Northern Ireland	212	120	— 92	—43
Iceland	275	141	—134	—49
Sweden	202	108	— 94	—47
France	167	140	— 27	—16
United States	94	67	— 27	—29
Canada	107	72	— 35	—33
England and Wales	129	111	— 18	—14
Scotland	197	173	— 24	—12
Norway	118	91	— 27	—23
Puerto Rico	294	235	— 59	—20

*Data relating to the 20 State capitals and Rio de Janeiro, D.F.

uals remaining much longer as patients, which has undoubtedly strongly contributed to increase the number of "existing cases."

The means of diagnosis and treatment at present available could really shorten the duration of the disease. Unfortunately, however, as we have already indicated, an early diagnosis is made in a reduced number of cases so that the majority of patients submitted to treatment is made up of patients with advanced forms of the disease, almost always "irrecoverable chronics," but capable of surviving for quite a long time due to the action of chemotherapy. These facts, which have no doubt exercised a great influence in the increase of prevalence, are perhaps sufficient to jeopardize the hypothesis of greater error in the calculation, as it was not possible to make use of the data relating to cures which may have been effected.

Case-Fatality-Rate

The measure of risk of death to which patients were subject during the period 1946-1954 shows that this, too, decreased considerably. In 1946 there occurred 17,135 deaths among 25,745 patients, while in 1954 there were 7,729 deaths among 56,674 tuberculosis patients.

The average death rate from tuberculosis in the State capitals and in Rio de Janeiro, D.F. thus fell from 66.5 in 1946 to 13.6 in 1954.

There is no doubt that the case-fatality rate calculations have been subject to the same causes of error observed in relation to morbidity. Data, however, coincide with certain facts connected with mortality, and which have already been related.

The percentual variation, for instance, was also greater in 1952 and 1953, with less 24.0 and 33.6 respectively, and did not go beyond 12.8 in 1954.

Applying these facts to the population of patients we verify that absolute differences among rates, which in the preceding year was 7.4 in 1952 and 7.9 in 1953, were not more than 2.0 in 1954.

Since it is known that case-fatality-rate in tuberculosis hospitals in Brazil in the same period showed the same decline, despite hospitalized patients being, in the majority of cases, bearers of serious forms of

TABLE VII

RIO DE JANEIRO, D.F.

NUMBER AND PERCENTAGE OF "POSITIVE" REACTIONS FOUND IN PERSONS SUBMITTED TO TUBERCULIN TESTS ACCORDING TO SOME AGE GROUPS

Age (Years)	1950			1955		
	Positive		Total	Positive		Total
	Number	Per Cent		Number	Per Cent	
0- 4	508	52.9	960	238	17.7	1,347
5- 9	833	71.0	1,173	381	40.9	932
10-14	752	78.4	959	547	57.7	948
15-19	627	83.1	754	3,852	72.1	5,342
Other ages	1,249	95.8	1,303	5,389	82.4	6,543
TOTAL	3,969	77.1	5,149	10,407	68.9	15,112

tuberculosis, we think results obtained may be utilized at least while better statistical data is not available.

Infectiousness

Sufficient data is not at present available for a comparative study of tuberculosis infectiousness in all the Brazilian capitals, many of which have withdrawn from their programs, with evident harmful consequences, even the surveys which every year were carried out in certain groups.

Results obtained in surveys carried out in 1950 and 1955 by the "Dispensário Escola" of the NATC in Rio de Janeiro, D.F., however, show that indices of tuberculosis infectiousness have also fallen in all age groups.

The percentage of positive reactors in relation to the total number of persons examined fell from 77.1 in 1950 to 68.9 in 1953, i.e., a reduction of merely 10.6.

In the age groups 0-4, 5-9 and 10-14, however, the decrease verified among the percentuals of infected patients was rather marked, especially in the first two, where the variation was 66.6 and 42.4 per cent respectively (Table VII).

This reduction in the indices of positive reaction to tuberculin precisely in the groups where the BCG vaccine must have been utilized in larger scale, may constitute an indication that the risk of infection tends to decrease.

Since it is known that populations free themselves of tuberculosis in view of the decrease of contagion opportunities, and that indices of infection represent the degree of dissemination of tuberculosis in a given region, we deem it opportune to start anew surveys in all Brazilian capitals, so as to render possible a better and more precise evaluation.

The Problem of Tuberculosis

Given the innumerable causes of error, the information revealed by the data in hand does not permit us to form yet a firm judgment of the problem of tuberculosis in Brazil.

We must, however, take advantage of it, since other sources of information are not at present available.

From the analysis made it is noted that the epidemiology of tuberculosis is undergoing such rapid modification that in any case it would be unsafe to put forth, at present, definite conclusions regarding the facts observed.

Everything, however, would seem to indicate that, despite the improvement observed not only with regard to mortality and case-fatality, but also in relation to incidence and even infectiousness, the present picture of tuberculosis epidemiology in this country is still rather serious.

The rise in mortality and morbidity rates verified in the last two years in several Brazilian capitals serve as a reminder to extreme optimists.

The prevalence of the disease points towards the magnitude of the problem which administrators and experts will have to face.

Therefore, if it was already considered a mistake to think that it was no longer necessary to continue utilizing all the methods of control, every means in the fight against tuberculosis, now we may consider it a mistake

of unforeseeable consequences, since the disease became, as it appears, susceptible of being reduced in even more considerable proportions.

SUMMARY

Mortality from tuberculosis in all the Brazilian capitals was reduced by 65.5 per cent between 1946 and 1954, this reduction representing the survival of almost 60,000 people.

The smallest number of deaths was registered in São Paulo, with 36.0 per 100,000 inhabitants.

The decline of mortality did not make itself felt with equal intensity in all stages of life, and was more marked in the age groups ranging from 10 to 14 and 15 to 19, with 80.0 and 90.5. The decrease was, likewise, greater among females.

The sharp fall recently observed in mortality rates would seem to have resulted from the use of new therapeutic agents.

In the period 1946-1954 there was a decrease of 46.9 in incidence. Case-fatality rate also decreased. There was, however, an increase of 77 per cent in prevalence, and in 1955 mortality itself increased by 14.7 per cent as compared to the previous year.

The epidemiology of tuberculosis is undergoing such rapid modification that it would be unsafe to draw definite conclusions based on the facts observed. It would appear, however, that despite the improvement observed, not only with regard to mortality and case-fatality, but also with relation to incidence and infectiousness itself, the present picture of tuberculosis epidemiology in Brazil is still serious.

RESUMEN

La mortalidad por tuberculosis en el Brasil, se ha reducido en 65.5 por ciento desde 1946 a 1954, lo que representa una sobrevida de 60,000 personas.

El número más reducido de muertes se registró en Sao Paulo, con una proporción de 36.0 por 100,000 habitantes.

La declinación de la mortalidad no se hizo notar en igual grado en todas las edades de la vida y fué más acentuada en los grupos de 10 a 14 y de 15 a 19 años con 80.0 y 90.5 por ciento. Además el descenso de la mortalidad fué más marcado en las mujeres.

El rápido descenso de la mortalidad bien puede atribuirse al uso de los nuevos agentes terapéuticos.

En el período de 1946-54 hubo un descenso de 46.9 en la incidencia. La mortalidad entre los casos (letalidad) también decreció. Sin embargo, hubo un aumento de 77 por ciento en la prevalescencia, y en 1955 la mortalidad misma aumentó 14.7 por ciento en comparación con el año anterior.

La epidemiología de la tuberculosis está sufriendo tan rápida modificación, que sería poco seguro extraer conclusiones definidas basándose en los hechos observados. Parece sin embargo que a pesar de la mejora observada no sólo respecto de la mortalidad sino de la letalidad y además en la relación de la incidencia y la infecciosidad, el cuadro presente de la epidemiología de la tuberculosis en Brasil, es aún serio.

RESUME

La mortalité par tuberculose dans toutes les capitales Brésiliennes fut réduite de 65,5% entre 1946 et 1954, cette réduction représentant une survie de presque 60.000 personnes.

Le plus petit nombre de décès fut enregistré à Sao Paulo avec 36 pour 100.000 habitants.

Le déclin de la mortalité n'a pas eu son effet avec une égale intensité pour toutes les périodes de la vie, et il est plus marqué chez les groupes âgés de 10 à 14 ans, et de 15 à 19 ans, avec respectivement 80 et 90,5%. La diminution fut aussi plus grande pour le sexe féminin.

La chute importante récemment observée dans les taux de mortalité semblerait résulter de l'emploi de nouveaux agents thérapeutiques.

Dans le période 1946-54, il y eut une diminution de 46,9% pour les nouveaux cas. Le taux de morbidité décrut également. Cependant en 1955 la mortalité augmenta de 14,7% par rapport à l'année précédente.

L'épidémiologie de la tuberculose est en train de subir des modifications avec une telle rapidité qu'il serait dangereux de tirer des conclusions définitives basées sur les faits observés. Il semble cependant, malgré l'amélioration observée, non seulement en ce qui concerne la mortalité et la morbidité et la morbidité mais également la fréquence des nouveaux cas et leur caractère infectieux, que le tableau actuel de l'épidémiologie de la tuberculose est encore sérieux au Brésil.

ZUSAMMENFASSUNG

Die Tuberkulosesterblichkeit in allen brasilianischen Haupt städten verringerte sich

um 65,5% in den Jahren zwischen 1946 und 1954; dieser Rückgang bedeutet, dass nahezu 60.000 Menschen am Leben blieben.

Die niedrigste Sterblichkeitsziffer wurde in Sao Paulo verzeichnet mit 36,0 auf 100.000 Einwohner.

Der Abfall der Sterblichkeit machte sich nicht in allen Lebensstufen mit gleicher Intensität fühlbar-. Er war ausgeprägter in den Altersgruppen von 10 bis 14 und 15 bis 19 Jahren mit 80,0 und 90,5. Die Abnahme war vergleichsweise stärker bei Frauen.

Der starke Rückgang der Sterblichkeitsziffer, wie er in jüngster Zeit beobachtet wurde, scheint die Folge von Verwendung neuer therapeutischer Stoffe zu sein. Für die Periode von 1946 bis 1954 ergab sich ein Verringerung des Vorkommens von 46,9. Auch die Fall-Sterblichkeit ging zurück. Allerdings kam es zu einer Zunahme der Krankheitshäufigkeit von 77%, und im Jahre 1955 stieg die Mortalitätsziffer selbst um 14,7% im Vergleich zum Vorjahr.

Die Epidemiologie der Tuberkulose unterliegt einem so rapiden Wandel, dass es bedenklich wäre, definitive Folgerungen auf der Basis der beobachteten Tatsachen zu ziehen. Es hat jedoch den Anschein, dass trotz der festgestellten Verbesserungen, nicht nur hinsichtlich der Mortalität und Fall-Sterblichkeit, sondern auch bezüglich der Häufigkeit und Infektiosität-, der gegenwärtige Standder Tuberkulose-Epidemiologie in Brasilien noch immer ein ernster ist.

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Experimental Silicosis: The Inhibitory Effect of Iron

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In 1932 Kettle[1] reported that where quartz particles are coated with iron their fibrogenic action is inhibited. Although initially unsuccessful,[2] Gardner was able to confirm this inhibitory action in 1938.[3] More recently Vorwald[4] also described the inhibitory action of iron on experimental silicosis in guinea pigs. Finely divided metallic aluminum powder according to Denny et al.,[5] and aluminum hydroxide according to Gardner[2] also inhibit experimental silicosis. Gardner[2] concluded that no inhibition could occur unless the inhibiting substance was within the same macrophage as the quartz particle it inhibited.

It is the purpose of this paper to describe the topographic relationship of the iron and silica in the lungs of rats and guinea pigs in which experimental silicosis had been inhibited by iron, and to discuss certain findings which appear to be at variance with the above-mentioned conclusion of Gardner[2] concerning this inhibition.

Method

The silica was ground flint which was reduced to a size approximating 3 micra in a micronizer. The ground flint was suspended in water and under a pressure of 40 p.s.i. was forced through a fine nozzle of an atomizer at near-sonic velocity against a hardened tool-steel baffle, causing the particles to be broken into smaller fractions. It was apparently during this treatment that the silica became contaminated with iron. The vapor and suspended silica dust were passed next through an impinger which removed most of the coarser particles. The outflow from the impinger passed through an inhalation chamber and from there through electrostatic precipitators. The silica from the precipitators was used for intratracheal injections.

By x-ray diffraction the silica dust consisted of 84 $\pm$ 6 per cent α quartz and the rest, of micaceous material. No iron was found. By chemical analysis, however, 8-9 per cent of the material was found to be iron. The failure to detect the iron by x-ray diffraction must be attributed to its noncrystalline state.

By electron microscopy the average particle size of the silica was found to be 0.1 micra.

For control, the silica was treated with concentrated hydrochloric acid and washed with water until the silica and the wash water failed to react with acidified potassium ferrocyanide.

Both types of silica were suspended in water so that 1 ml. contained 25 mg. dust. One group of rats was injected intratracheally with 1 ml. of

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the iron-contaminated quartz and another group of rats was similarly injected with the iron-free quartz. Some animals died immediately or within 24 hours after the injection. Others died at various times from intercurrent disease. Pairs of animals were killed for sampling at various intervals up to 16 months following the injection.

Guinea pigs were exposed to the iron-contaminated quartz dust in an inhalation chamber for six hours per day, five days per weeks, for one year. The dust concentration averaged 44 mg. per m.[3] Following the dust exposure these animals were pastured for another year. At various intervals animals were killed for sampling.

The lungs of all animals, whether dead of intercurrent disease or killed for sampling, were prepared for microscopic study by inflating the lungs with formalin at a pressure of 10 cm. water. Paraffin sections were prepared and stained with H. and E. Replicate sections were stained for iron by the potassium ferrocyanide method and counterstained with van Gieson's stain. The topographic relationship of silica was demonstrated by the author's recently published photographic method.[6]

Results

Rats:

Initially the iron was very closely associated with the silica although negligible amounts of iron and silica were found to be independent of one another. Three months after the injection of the iron-contaminated silica the lungs contained scattered cellular aggregates or small nodules which showed no indication of collagen formation. These were apparently attached to alveolar walls or situated about vessels. They contained a scanty amount of iron as gauged by the diffuse green coloration of the nodules. The intensity of the color varied from one nodule to the next and was not necessarily uniform thoughout the same nodule. The silica content of the nodules on the other hand was high regardless of the low iron content.

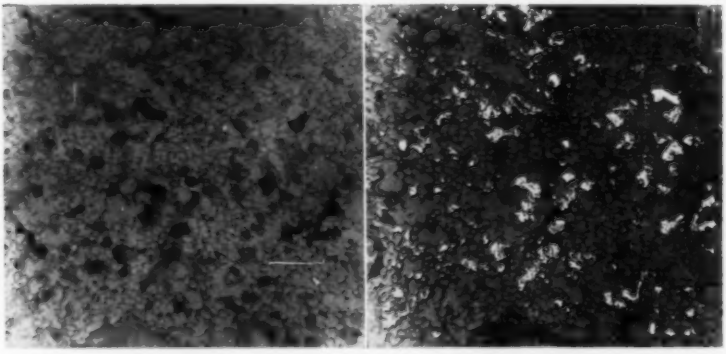

FIGURE 1 FIGURE 2

Figure 1: Rat 2307 killed six and one half months following an intratracheal injection of 25 mg. iron-contaminated silica. In this lung tissue there is an abundance of nodules which are cellular and contain no collagen. The iron content (indicated by black) varies from nodule to nodule and within the same nodule. van Gieson-potassium ferrocyanide stain. (Red filter) x 39.—*Figure 2:* Composite of the above showing a remarkably uniformly high silica content of the nodules in spite of their variable iron content. x 39.

This finding is, in effect, evidence of the dissociation of iron from the silica. Nearby air spaces contained scattered or clustered alveolar macrophages most of which took a deep blue stain indicative of a high iron content. Although a few siderotic macrophages appeared to be free of silica, most of them contained appreciable amounts of the latter.

In comparison, the control animals injected with iron-free silica showed nodules which at one month were as large as, or larger than, and as numerous as, those of the iron-contaminated silica group at three or four months after the injection. Whereas at six months following injection the nodules of control animals showed a moderate collagen content along with a fair cellularity, the nodules secondary to iron-contaminated silica were considerably smaller, more cellular, and contained little or no collagen.

Rats dead or killed 11 to 16 months after the injection of iron-contaminated silica demonstrated many well-collagenized nodules which generally contained no iron. Even those nodules only partially collagenized, with few exceptions, contained no iron. The exceptional nodule stained only faintly for iron. The silica content of the well-collagenized nodules was frequently less than that of the more cellular ones. A few scattered or clustered alveolar macrophages were present in air spaces near the nodules. These macrophages contained a small amount of iron, generally associated with silica. The essential difference at this time between the animals injected with iron-free silica and those injected with iron-contaminated silica was a greater number of nodules and larger masses of confluent nodulations in the former.

The tracheal lymph nodes of the control animals showed collagenization which was moderate at three months and progressed rapidly thereafter. Coincident with the collagenization there was an abundance of silica demonstrable in the lymphoid tissue. In the rats injected with iron-contaminated silica the collagenization of the lymph nodes was greatly de-

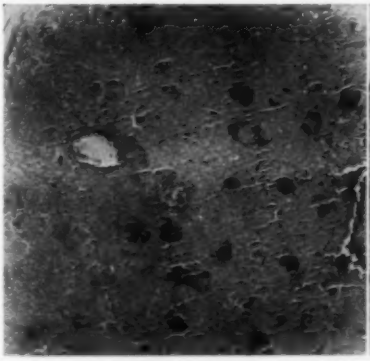

FIGURE 3

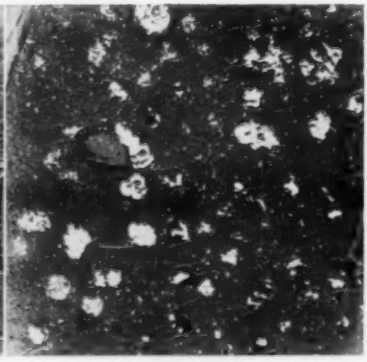

FIGURE 4

Figure 3: Rat 2305 killed three and one half months following an intratracheal injection of 25 mg. iron-contaminated silica. Section of tracheal lymph node shows rounded foci of large, pale cells. The periphery of these foci stains heavily but irregularly for iron (darker shade). No collagen is present. van Gieson-potassium ferrocyanide stain. (Red filter) x 100.—*Figure 4:* Composite of the above showing a generally high silica content of the foci. There is obvious dissociation of iron and silica. Some foci rich in iron contain little silica and the centers of the foci that contain little or no iron, are rich in silica. x 100.

layed. At three to four months after the injection the lymph nodes contained small, discrete endothelial foci—but no collagen. The peripheral portions of these foci were rich in iron as well as in silica. At 11 to 16 months after the injection collagenization of the lymph nodes was well advanced, with some exceptions however. The collagenized nodes contained abundant silica but little or no iron. Where iron was present it was associated with silica. The exceptions, where collagenization of the nodes was absent, contained little silica and little iron in spite of the presence of well-defined pulmonary nodulations.

Guinea Pigs:

The pulmonary response to the inhalation of iron-contaminated silica dust was notably different than the intratracheal injection of the same dust in rats. The reaction in guinea pigs consisted of proliferation of alveolar cells which desquamated so as to fill many of the air spaces with cells or their debris or both. This was associated with a non-collagenous thickening of alveolar walls, consisting of swelling and of proliferation of alveolar lining cells as well as interstitial edema. The entire lung was not uniformly affected. In the early state there were widely separated, relatively small foci of this involvement. With continued exposure the foci became larger and more numerous. The macrophages stained strongly for iron throughout the 12-month exposure period but the iron content gradually diminished during the second year so that at the end of this time there were many foci which contained little or no iron. However, some demonstrable iron persisted in scattered foci. The silica content of the air spaces remained high irrespective of the diminishing iron content and regardless of whether the alveolar content consisted largely of well-preserved cells or merely of cellular debris. Toward the end of the second year scattered small silica dust aggregates were found within the thickened alveolar walls. This alveolar wall thickening was very pronounced and widespread at this time.

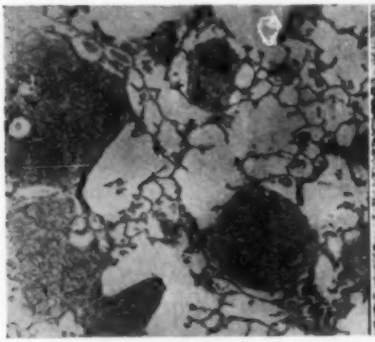

FIGURE 5

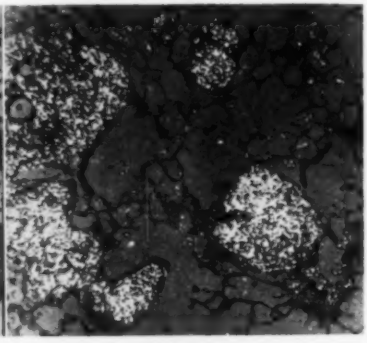

FIGURE 6

Figure 5: Rat 2460 killed thirteen and one half months following an intratracheal injection of 25 mg. iron-contaminated silica. Section of lung exhibits rounded, moderately collagenized nodules which contain no iron. The only iron is found within alveolar macrophages in the lower right corner. van Gieson-potassium ferrocyanide. x 100.—*Figure 6:* Composite of the above showing abundant silica within the nodules. Silica is also present within the iron-containing alveolar macrophages in the lower right corner. x 100.

Cellular aggregates leading to the formation of nodules never developed in these animals. With some exceptions no collagen formation was demonstrable in the lungs even at the end of the second year. The exceptions were represented by several of the animals killed at the termination of the experiment in which a number of foci were found whose thickened alveolar walls contained coarse collagen fibers. Such alveolar fibrosis was not widespread; it was associated with abundant iron-free silica in adjoining air spaces. A puzzling observation was a similar abundance of iron-free silica elsewhere where no collagen was present.

Although foci of hyalinized collagen were found in the tracheal lymph nodes of some guinea pigs dead or killed six to 11 months following the last exposure to the iron-contaminated silica dust, no collagen was found in the tracheal nodes of other animals killed four to 12 months following the last exposure to the same dust. Iron was not demonstrable in either the nodes with fibrosis or those in which collagen was absent, but an abundance of silica was present in all nodes.

Discussion

The parallelism which exists in rats between the presence of iron and the inhibition of collagen formation is not found to the same degree in the guinea pig. In the latter, although inhibition of collagen production is demonstrable in the presence of iron, this inhibition appears to persist in the *absence* of demonstrable iron. Yet, even in the guinea pig this inhibition may not be absolute inasmuch as greatly delayed focal collagenization of alveolar walls occurred in several animals.

It is interesting that in rats the formation of silicotic nodules is not inhibited by the iron, only the collagenization of these nodules is retarded. In guinea pigs, however, the contaminating iron completely prevents the formation of silicotic nodules.

It has recently been demonstrated that most experimental silicotic nodules in the lung form upon alveolar walls by focal proliferation of alveolar cells which remain coherent.[7]

Accordingly, the difference in the effect of the iron-contaminated quartz dust upon the rat lung as compared with the effect of the same dust upon the guinea pig lung may be a relatively simple one but, nevertheless, one which determines whether silicotic nodules will or will not form. This difference, in effect, involves the cohesion or the lack of cohesion of the proliferated alveolar cells. In guinea pigs, it appears

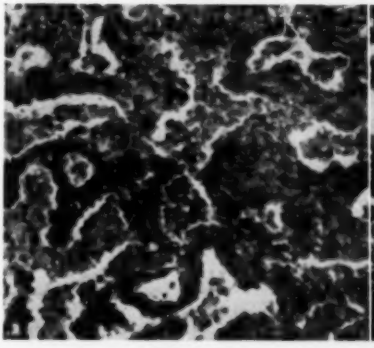

FIGURE 7

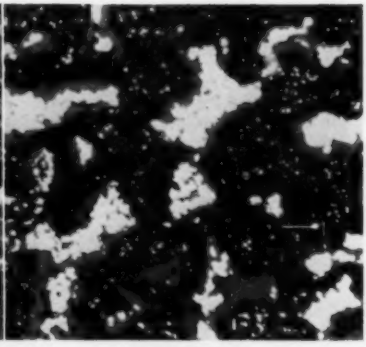

FIGURE 8

Figure 7: Guinea pig 176 killed 12 months after completion of a 12-month exposure to iron-contaminated silica dust in an inhalation chamber. The lung contained no nodules. This field shows the characteristic profound proliferation and desquamation of alveolar cells with non-collagenous alveolar thickening. Collagen is absent in spite of the fact that no iron is demonstrable. van Gieson-potassium ferrocyanide. x 297.—*Figure 8:* Composite of the above showing the heavy silica content of alveolar macrophages and debris. A sparse distribution of small silica aggregates within thickened alveolar walls is also indicated. x 297.

that such cellular cohesion is lacking and that the proliferated alveolar cells desquamate to cause obstructive accumulations of cells and debris within air spaces.

That a slight degree of dissociation of iron from the silica apparently occurs is indicated by the demonstration of iron which is not associated with silica. It is difficult, however, to rule out endogenous iron even though iron is rarely demonstrable in the control animals. The disappearance of the iron occurs more promptly from the silicotic nodules in rats than from the alveolar cells and debris in guinea pigs. This disappearance seems to be caused by a gradual dissolution of the iron.

The fact that silica devoid of demonstrable iron is found in guinea pig lungs and lymph nodes where no collagen is present appears to contradict Gardner's premise[2] (applied to aluminum) that the inhibiting substance must occupy the same cell as the silica in order to inhibit the biologic action of the latter.

Perhaps the solution of the problem concerning the mechanism of this very interesting inhibition of *experimental* silicosis by iron and aluminum may lie in a possible effect of these metals upon the cohesiveness of proliferating cells and upon a possible interference by these metals with antigen-antibody reactions. The latter is suggested by papers published from Vigliani's laboratory[8, 9] which indicate that silicotic nodules contain in addition to collagen also globulins of the type found as a result of antigen-antibody reactions.

SUMMARY

The inhibition of the fibrogenic action of quartz dust by associated iron, initially reported by Kettle and later confirmed by Gardner and Vorwald has been reconfirmed.

In rats, this inhibition was temporary, serving to delay the maturation of silicotic nodules by a few months only.

In guinea pigs, iron completely prevented the formation of silicotic nodules but it did not inhibit completely the development of collagen within thickened alveolar walls.

In rats, the development of collagen within silicotic nodules paralleled the disappearance of iron from these sites. In guinea pigs, the iron had also disappeared from those regions in which collagen had developed. Yet, there were other foci in which there was manifest inhibition of collagen formation in spite of the fact that abundant iron-free silica was demonstrable in such regions.

This apparent inhibition of fibrosis in the absence of iron contradicts Gardner's premise (applied to aluminum) that the inhibiting substance, to be effective, must occupy the same cell as the quartz particle which it inhibits.

RESUMEN

La inhibición de la acción fibrógena del polvo de cuarzo por la asociación de hierro, se ha vuelto a confirmar después de haberse conocido por los informes de Kettle primero, y después por Gardner y Vorwald.

Esta inhibición fué temporal en las ratas, sirviendo para retardar la maduración de los nódulos silicosos sólo por pocos meses.

En los cuyes el hierro evitó completamente la formación de nódulos silicosos, pero no lo hizo completamente para el desarrollo de substancia colágena dentro de las paredes alveolares engrosadas.

En las ratas el desarrollo de colágena dentro de los nódulos silicosos fué paralela a la desaparición del hierro en esos sitios. En los cuyes, el hierro también había desaparecido de esas regiones donde la colágena apareció. No obstante hubo manifiesta inhibición de la aparición de colágena en otros focos a pesar de que pudo demostrarse abundante sílice sin hierro en esas regiones.

Esta aparente inhibición de la fibrosis en ausencia de hierro contradice la premisa de Gardner (aplicada al aluminio) de que la substancia inhibidora debe ocupar la misma celdilla que la partícula de cuarzo cuya acción inhibe.

RESUME

L'inhibition de l'action fibrogène de la poussière de quartz par adjonction de fer, primitivement rapportée par Kettle et plus tard confirmée par Gardner et Vorwald, a été confirmée de nouveau.

Chez les rats, cette inhibition fut temporaire, servant à retarder la maturation de nodules silicotiques de quelques mois seulement.

Chez les cobayes, le fer empêcha complètement la formation de nodules silicotiques, mais n'inhiba pas complètement le développement de collagène à l'intérieur des parois alvéolaires épaissies.

Chez les rats, le développement de collagène à l'intérieur de nodules silicotiques fut parallèle à la disparition du fer de ces localisations. Chez les cobayes, le fer avait également disparu des zones dans lesquelles le collagène s'était développé. Cependant, il y avait d'autres foyers dans lesquels il y avait une inhibition manifeste de la formation de collagène bien qu'on puisse mettre en évidence dans ces localisations d'abondantes particules de silice dépourvue de fer.

Cette inhibition apparente de la fibrose en l'absence de fer est en contradiction avec les conclusions de Gardner (concernant l'aluminium) selon lesquelles la substance

inhibitrice, pour être efficace, doit occuper la même cellule que la particule de quartz qu'elle inhibe.

ZUSAMMENFASSUNG

Es wurde erneut die Hemmung der bindegewebsbildenden Wirkung von Quarzstaub durch assoziiertes Eisen bestätigt wie sie zuerst mitgeteilt worden ist von Kettle und später bestätigt von Gardner und Vorwald.

Bei Ratten war diese Hemmung temporär und reichte nur hin, die Bildung der silikotischen Knötchen einige Monate zu verzögern.

Bei Meerschweinchen verhinderte Eisen in vollem Umfang das Auftreten von silikotischen Knötchen; aber es verhinderte nicht vollständig die Entwicklung von Collagen innerhalb der verdickten Alveolarwände.

Bei Ratten ging die Entwicklung von Collagen im inneren von silikotischen Knoten parallel mit dem Verschwinden des Eisens an diesen Stellen. Bei Meerschweinchen war das Eisen auch verschwunden aus den Zonen, in denen sich Collagen entwickelt hatte. Doch fanden sich andere Herde, in denen sich eine Hemmung der Collagenbildung zeigte trotz der Tatsache, dass reichlich eisenfreies Silicium in solchen Gebieten nachweisbar war.

Diese augenfällige Hemmung der Fibrose bei fehlendem Eisen widerspricht Gardner's Prämisse bezogen auf Aluminium, wonach die hemmende Substanz, um wirksam zu sein, dieselbe Zelle ausfüllen müsse wie die Quarzpartikel, die es hemmt.

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Tracheo-Esophageal Fistula and Esophageal Atresia

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Congenital atresia of the esophagus was first described in 1697 by Gibson, who was a grandson of Oliver Cromwell, and physician-general to the army. Neither the clinical history nor the physical findings have changed since his often quoted classical description. It was 245 years later before success was recorded in the management of the condition. Cameron Haight[8] in 1941 first established esophageal continuity successfully in one stage operative procedure, by primary anastomosis of the proximal and distal segments of the esophagus.

The delayed progress in the treatment of the condition was due, in the past, to the misconception that the condition was extremely rare. Guthrie, in searching the records of the Royal Hospital for Sick Children, Glasgow, found 24 proved, and a further six probable, cases in 6,916 necropsies. The late Sir G. Grey-Turner estimated that the malformation occurred about as frequently as hare-lip and cleft palate. At the Postgraduate Medical School of London four cases of atresia were found in 10,543 deliveries (1 in 2,635 deliveries).

It is quite conceivable that the incidence is higher than 1 in 2500 births. Many cases probably are not recognized as such and the deaths are regarded as having been due to atelectasis or pneumonia, without a confirming autopsy.

That the condition can be overlooked is easy to understand, particularly when the infant is not supervised by a pediatrician. The early signs are not always definite or even recognizable. The infant brings up some frothy mucus during the first day or two of life. Attempts at feeding lead to regurgitation, choking and probably cyanosis. Excess of mucus in the naso-pharynx occurs in normal infants, but aspirations soon relieve any cyanosis which may have been present.

Without the diagnosis and treatment of atresia of the esophagus, pulmonary symptoms usually develop by the second day. This may be diagnosed as pneumonia, and further feeding troubles and respiratory distress attributed to the respiratory infection. With the fatal termination in a week or more, even if necropsy is performed, it is quite conceivable that the diagnosis may be overlooked. The burden of early recognition falls largely on the obstetrician, the pediatrician, and the nursing personnel of the new-born nursery. If they are suspicious regarding any child who has excess mucus, episodes of cyanosis, and who does not take fluid properly in the new-born period, more of these cases will be recognized earlier than at present, before a great deal of aspiration has occurred. There is no real substitute for awareness and careful observation.

Although the diagnosis may be made frequently on history alone, physical signs and X-ray film examination are usually necessary to confirm it. The diagnosis is confirmed, when suspected, by the passage of a soft rubber No. 10 or 12 F catheter through the mouth into the pharynx and proximal esophagus. The catheter will be held up 8 to 10 centimeters from the alveolar margin in the usual type of atresia.

To gain positive proof of the anatomic abnormality which is present, a few simple roentgenographic studies are helpful. A straight antero-posterior film of the chest is done to determine the state of the lung fields. Almost all show signs of atelectasis or aspiration pneumonia, characteristically in the right upper lobe. The catheter is again passed into the upper esophagus, and 0.5 to 1.0 cc of iodized oil is injected and its course followed by fluoroscopy. The iodized oil is left in position for a short time to see if any passes through an upper fistula, then is withdrawn. Barium should never be used, as aspiration into the air passages results in a chemical type of pneumonia. The presence of air in the gastrointestinal tract, as shown by x-ray film, is clear-cut evidence of the presence of fistula between the tracheo-bronchial tree and the lower segment of the esophagus. Its absence, however, though suggestive, is not a sure sign of the absence of such a fistula. Fistulae between the upper pouch and the trachea are usually impossible to demonstrate, except by operative dissection.

Embryology

To understand the development of congenital tracheo-esophageal fistula and other anomalies of the esophagus it is necessary to review briefly the embryology of the trachea and esophagus. Both these structures develop from part of the foregut. By about the fourth week a definite esophagus has developed as a short tube extending from the pharynx to the stomach. At seven weeks the epithelium thickens by proliferation, then vacuoles appear in it, and in this way the lining becomes irregularly channeled. In the embryos of 3 mm. the laryngotracheal groove appears in the floor of the gut, just caudal to the pharyngeal pouches. This groove deepens and splits off the primordium which is to become pharynx, trachea and lungs. With the close association of the trachea and esophagus in development, it is easy to see how tracheo-esophageal fistula can occur.

Conditions Which Influence Survival and Prognosis

Associated Anomalies: The possibilities of other anomalies associated with atresia of the esophagus must always be considered. Probably the

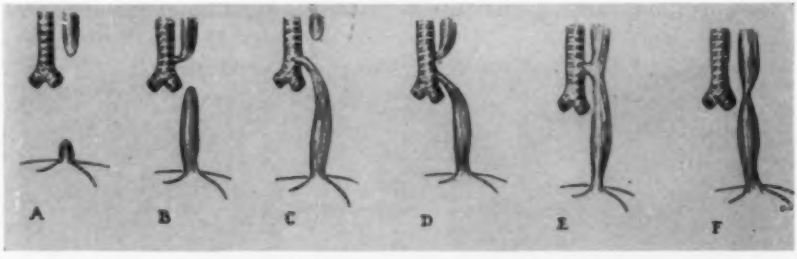

FIGURE 1: Types of congenital abnormalities of the esophagus. A. Esophageal atresia. No esophageal communication with the trachea. Under such circumstances the lower esophageal end is very apt to be quite short. B. Esophageal atresia, the upper segment communicating with the trachea. C. Esophageal atresia, the lower segment communicating with the back of the trachea. Over 90 per cent of all esophageal malformations fall into this group. D. Esophageal atresia, both segments communicating with the trachea. E. Esophageal has no disruption of its continuity, but has a tracheo-esophageal fistula. F. Esophageal stenosis. (Courtesy from Gross: *Surgery of Infancy and Childhood*, W. B. Saunders Company, Philadelphia, 1953.)

majority of these babies have no other important anomalies, but a considerable group have abnormalities which are of an equally serious nature. Congenital heart disease, malformations of the anus and rectum, duodenal obstruction and Meckel's diverticulum are among the commonest associated lesions. Recognition of their existence is imperative to plan a successful surgical attack. Gross[7] found in 233 patients with atresis of the esophagus, 77 had various anomalies, some babies had several. Humphreys et al.[9] in 136 patients found 75 with other congenital malformations, and two-thirds of the infants who died post-operatively were handicapped by other anomalies. Ladd and Swensen (1947) found that of their 82 cases, only 18 had serious additional abnormalities, and these were chiefly in the heart.

Obviously, secondary operations in these precarious infants raises the mortality rate, but from a perusal of the literature, a considerable number of infants have survived the correction of the additional deformities.

Prematurity: There seems to be a higher incidence of prematurity with this type of anomaly than in other malformations of the body. Approximately 25 per cent of these infants are less than five pounds in weight. Prematurity added to pulmonary complications greatly increases the risk of surgery to these vulnerable infants. Humphreys et al.[9] attempted in their 136 cases to relate mortality following surgery at birth weight. They found that prematurity, as judged by weight, though a determining factor at the lower extremes of size, did not preclude survival.

Delay in Diagnosis: This is probably the largest single factor in contributing to the mortality rate of the condition. An infant who comes to major surgery exhausted, and with an overwhelming pulmonary infection, is obviously a bad risk, in spite of the best pre-operative preparation. Probably most infants where the diagnosis has been delayed for four days or more, will not survive surgery, in spite of all measures. Cases that are diagnosed in the first few hours or the first day, should be brought to operation immediately. After the first day, much can be gained by an appropriate period of preparation, to get the infant into better condition. Adequate time should be expended to correct ketosis, dehydration and pulmonary infection. This period may extend up to 12 hours. Awareness of the condition, early diagnosis, and prompt instigation of pre-operative

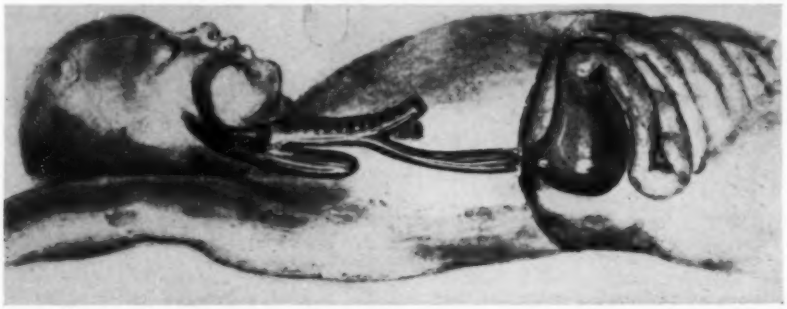

FIGURE 2: The common type of esophageal malformation. There is esophageal atresia. The upper pouch ends blindly. The lower pouch communicates with the back of the trachea, just at or slightly above its bifurcation. (Courtesy from Gross: *Surgery of Infancy and Childhood*, W. B. Saunders Company, Philadelphia, 1953.)

measures will greatly enhance the infant's chance of successful surgery. The mortality will be less if the operation is done as soon as possible after birth.

Pre-operative Care: This is most important, and a pediatrician should be in attendance. When the condition is suspected, after passage of a soft rubber catheter into the proximal esophagus, it is our opinion, from experience with over-zealous radiologists, that opaque media should not be used to confirm the diagnosis. Iodized oil that overflows or is introduced into the tracheo-bronchial tree is hazardous to an already embarrassed system. One can obtain a satisfactory contrast x-ray film by simply distending the upper pouch with air and avoiding soilage of the lungs.

The infant is placed in an incubator or isolette and moist oxygen administered with controlled temperature. The pharynx is suctioned with a soft rubber catheter every 15 to 30 minutes. The potential of the bacterial content in the upper stump of the esophagus should be emphasized. It often has a high content of anaerobic streptococci. Penicillin and streptomycin plus a wide spectrum antibiotic should be administered. Of recent years we have been making more frequent use of tracheal suction in order to prepare these cases for surgery and carry them past the crucial phase in the post-operative period. Respiratory complications are among the main lethal factors: and in their debilitated condition they are unable to satisfactorily clear their tracheo-bronchial tree. By means of a laryngoscope and catheter suction, introduced through the vocal cords, a simple and effective means is available to protect and drain the respiratory system and reduce mortality.

There is a good argument for nursing these patients in the Fowler's rather than the Trendelenburg position. The gastric secretion in the first few hours of life is highly acid, and the chemical pneumonia it produces on gaining entrance to the tracheo-bronchial tree through the distal fistula is added to that pneumonia already present from aspirated saliva and other liquids.

Adequate hydration should be maintained by intravenous fluids, which also correct ketosis. Great care should be taken to avoid overhydration. Infants that are jaundiced should receive vitamin K pre-operatively. Blood is obtained to the amount of 15 to 20 cc per pound, in preparation for operative procedure.

Operative Procedure

Provided a skilled anesthetist is available, intra-tracheal anesthesia, controlled respiration and a right trans-pleural approach, offers certain advantages over other methods of attack. Certainly this approach offers better visualization of the segments and an easier, time-saving anastomosis. It gives an excellent view from the top to the bottom of the chest, and it allows the widest possible dissection of the esophagus. It also permits opening of the diaphragm and mobilization of the stomach when this is required.

A standard postero-lateral incision is made, entering the pleural cavity through the right fourth interspace. The mediastinal pleura is entered by dividing the azygos vein, the bifurcation of the trachea is easily identified, and the fistulous communication with the distal esophagus dissected free. The distal esophagus may be mobilized to the hiatus of the diaphragm if

justified. The blood supply enters the esophagus from the medial aspect and can be preserved. In some instances it may be necessary to utilize the stomach intrathoracically for restoration of continuity. This can be readily accomplished through a right-sided approach. The fistulous connection between lower esophageal segment and the trachea is now severed, and the tracheal opening closed with fine interrupted silk sutures. Dissection of the well vascularized upper pouch high into the neck, should be extensive and painstaking, and complete separation of the pouch from the trachea, to which it is often densely adherent over a fairly long interval, should be accomplished. Occasionally a second fistula is found at this level. Wide dissection of the well-developed upper pouch is the best means of obtaining adequate length for the anastomosis without tension. Devascularization of this pouch is not a problem, as the main blood supply is from the inferior thyroid vessels.

A two-layer technique for the anastomosis, as described by Haight,[16] is used in most cases. After the muscularis has been dissected from the mucosal portion of the upper pouch, the latter is brought down and sutured at appropriate points to the opening in the lower esophagus, which can be enlarged to an adequate size if necessary before opening the mucosal pouch of the upper segment. After it is once anchored, the upper pouch is opened, and the anastomosis completed, using all layers of the lower segment. The cuff of muscularis from the upper pouch is then drawn downward over the inner suture line and sutured to the muscularis of the lower segment. Interrupted No. .5-0 silk sutures are used to avoid constriction at the line of anastomosis. After completion of the anastomosis, tension may be relieved by suturing the proximal pouch to the para-vertebral fascia. The mediastinal pleural flaps are closed over the anastomosis to reinforce this site, taking care to leave an open area at the lower end of the suture line for drainage.

Following closure of the chest wall and catheter drainage to an underwater-seal, it is our practice, if the infant's general condition is satisfactory, to establish an immediate gastrostomy. This is a tremendous help in putting the esophagus at rest, yet permitting adequate feeding. The gastrostomy can easily be delayed for 24 to 48 hours, and may be done under local anesthesia if desired.

Post-Operative Care

Post-operatively, the infant is returned to the isolette, and the high humidity and oxygen atmosphere. It is most important that the infant has constant nursing supervision. In our experience this is best obtained on a premature nursery ward. Frequent pharyngeal, and when indicated, tracheal, aspirations are continued. Carefully controlled intravenous fluid therapy is continued, bearing in mind that these children require very little fluid in the immediate post-operative period, and that over-hydration is a frequent cause of pulmonary edema and fatality in these cases. The gastrostomy tube is left open for 24 to 48 hours, to keep the stomach deflated. On the second or third day feedings can be cautiously started through the gastrostomy tube, starting with 10 per cent glucose and water in small quantities. Oral feedings are begun on the sixth to the eighth day, after satisfactory conditions are demonstrated by a iodized oil swallow.

The gastrostomy tube should be removed only when oral feedings have been well taken for at least one week and radiologically there is an adequate esophageal lumen.

Post-Operative Stricture

It is difficult to predict which subjects are going to develop stricture at the anastomotic site after discharge with a satisfactory radiological picture. That it can be a serious late complication is illustrated by fatalities in two of our cases after an excellent early surgical result. The later development of stricture may be due to prior leakage and mediastinitis. When the anastomosis has been done under great tension or the union has been poor, presumably stricture formation is likely to develop. It has generally been found that narrowing at the point of anastomosis has been most troublesome within the first year of life, requiring often, many dilatations. After this period the stricture seems to grow adequately with the esophagus, to necessitate only infrequent dilatations.

Early strictures that are visualized before the gastrostomy tube is removed are best treated by retrograde dilatation with small soft Tucker's dilators. Later strictures should be inspected under general anesthesia to determine the character of the tissue at the stricture site and subsequently dilated with a gum webbing type of dilator, passed after an attached filiform leader.

Most strictures require multiple instrumentation, though some are well treated by one dilatation. Occasionally a more radical attack is necessary,

FIGURE 3: The rare type E, from Gross's classification, showing the high trachea, fistulous communication between the esophagus and trachea, opposite the first and second thoracic vertebrae.

and excellent results have been obtained from a secondary operation, where removal of scar tissue and a re-anastomosis were performed, usually between one and two years of age.

Results

In 1956 we treated surgically 10 cases of tracheo-esophageal fistula. There were six long-term survivors of this group, although one of these subsequently died of acute staphylococcal pneumonia at the age of three months. Two of the deaths were due to stenosis at the site of anastomosis, occurring at six weeks and two months respectively. In one of these there was a sudden onset of dysphagia in an infant who had previously been swallowing quite well. The iodized oil swallow in this baby showed an almost complete obstruction. Death occurred from pneumonia after dilatation under general anesthesia. The second one had intermittent difficulty in feeding, with aspiration of feedings. A recurrence of fistula was suspected, but lipiodol swallow showed what appeared to be a normal esophagus. Death was due to pneumonia, and at autopsy a partial obstruction was found by a baffle of fibrous tissue at the site of anastomosis. This baby had developed a post-operative disruption of the suture line of the esophagus, with tension pneumothorax, which had been controlled by the insertion of an intercostal catheter. The other patients not surviving the immediate post-operative period died of pneumonia. One of these was operated on two days after birth, and the other eight hours after birth. Both were premature infants, and at autopsy both were found to have multiple abnormalities, including duodenal atresia in one case, and a large atrial septal defect in the other.

It is probably reasonable to conclude that there were in this series, 60 per cent survivors of the operative procedure for correction of congenital tracheo-esophageal fistula.

FIGURE 4: Pre-operative radiographic picture of Case 2. Note the unusual length of the upper pouch.

Of the surviving group there were two unusual cases, which are to be reported in detail. One of these is a type which, to our knowledge, has not been previously described.

Case Reports

Baby V.: Born May 5, 1956. Discharged June 6, 1956.

We were called in consultation on May 17th, following the iodized oil swallow which resulted in the radiological picture (Fig. 3). The infant's history had been briefly as follows: The second day after birth the attending nurse noticed the infant had stertorous breathing, and seemed to have excessive mucus. Examination at this time revealed moist rales in both lung fields, which were thought to be due to aspiration or atelectasis. Feedings resulted in moderate cyanosis, therefore the infant was fed by gavage of breast milk and supplemented with interstitials of glucose and saline. Terramycin was started on the third day of life.

This regime improved the infant's condition to some degree. However, on May 11, cyanosis became troublesome at gavage, and the infant was placed in a croupette. Abnormal amounts of mucus secretion and respiratory difficulty were prominent features until operative repair.

The x-ray film on May 17, easily established the diagnosis of tracheoesophageal fistula, without disruption of the continuity of the esophagus. Due to bilateral aspiration pneumonia and poor general condition of the infant, it was necessary to spend a further three days in trying to improve its desperate condition.

Surgery was performed on May 20, as rapidly as possible. As the fistula was high, opposite the first and second thoracic vertebrae, the upper four ribs were exposed through a right postero-lateral incision. The second rib was resected subperiosteally in the main, and the first and third ribs were shingled posteriorly. By gentle dissection, the parietal pleura was dissected off the chest wall and the apex of the lung depressed. The esophagus and trachea were cleaned and the fistula found with some difficulty. It ran tangentially downward from the esophagus to the trachea, opposite

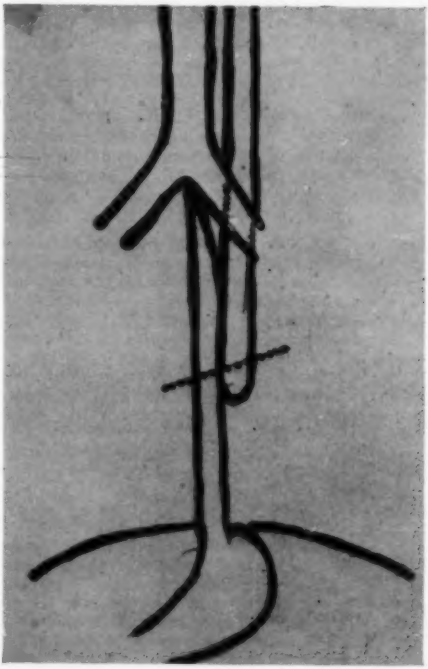

FIGURE 5: Schematic representation of the findings at operation in Case 2. It was realized after operative exposure that a right sided approach would have been easier. The aortic arch interfered with easy division of the fistula and closure of the same. However, from the pre-operative radiologic picture there was a suspicion of an atretic area of some length of the lower esophagus.

the first thoracic vertebra. It was divided and the ends closed with fine interrupted silk sutures. Following closure of the chest wall the post-operative condition was better than we expected. Intravenous fluids were continued until the fifth day and on the fourth day small amounts of sterile glucose feedings were taken by mouth. Subsequently, to our amazement, the child progressed rapidly toward normality. Although there had been a delay of fifteen days before the operative procedure, respiratory complications post-operatively were not of serious concern. A gastrostomy was not indicated in this case, we felt, because of the normal continuity of the esophagus.

The child was discharged from hospital on June 6, in good condition and has remained so since, gaining and developing normally.

Baby L.: This infant was a full term, six pound girl. Delivery was essentially normal, but there was some difficulty in making the child start breathing, and she was taken to the observation nursery. Here it was noted that there was an excessive amount of mucus, necessitating frequent aspiration of the pharynx. A tracheoesophageal fistula was suspected, and a catheter was passed into the esophagus. An obstruction was encountered somewhat lower than in the usual type of tracheoesophageal fistula. A small amount of lipiodol was injected through the catheter, and x-ray films taken. As is seen in Figure 4, the esophageal "pouch" extends into the lower one-third of the thorax. Because of this, it was decided to do a left, rather than a right, thoracotomy. At operation, eight hours after birth, it was found that there was a partial reduplication of the esophagus, with the lower segment communicating with the trachea, as is shown in the diagram. It was a simple matter to establish continuity of the esophagus, and obliterate the remaining fistulous tract into the trachea, with interrupted sutures. The post-operative course was quite uneventful. Oral feedings were commenced with glucose and water on the fifth post-operative day, and formula feedings begun the following day. Follow-up at six months of age showed the child to be normally developed for its age, and having no difficulty in swallowing.

SUMMARY

1. Since the outstanding contribution by Cameron Haight in 1941 in the surgical management of tracheoesophageal fistula and esophageal atresia, the picture has changed from one of almost invariably fatal outcome, to that of a high survival rate in the surgically corrected infants. Prematurity and associated anomalies are uncontrollable factors in this condition, but do not necessarily, in themselves, preclude a successful outcome. It is the awareness of the condition by doctors and the nursing profession, and the establishment of an early diagnosis that is stressed. If, following early diagnosis, proper pre- and post-operative care (including late post-operative supervision) is maintained, a recovery rate in the neighborhood of 70-80 per cent can be expected, where prematurity and concomitant anomalies are not a factor.

2. Reported here are two rare types of this anomaly, from our series of ten cases in 1956, with a 60 per cent survival rate.

RESUMEN

1. Desde que Cameron Haight en 1941 hizo su notable contribución al tratamiento quirúrgico de la fístula traqueo-esófágica y en la atresia del esófago el cuadro ha cambiado desde aquella época en que casi había resultado fatal invariablemente hasta ahora que hay un sobrevida en proporción elevada en los niños tratados quirúrgicamente. La prematuridad y las anomalías que le acompañan, son factores no dominables de esta anomalía, pero no por éso impide un resultado satisfactorio. Se recalca la importancia de que los médicos y las enfermeras estén alertas ante esta malformación.

Si después de hacerse el diagnóstico se hace un cuidado pre y postoperatorio bien mantenidos (incluyendo el postoperatorio tardío), es de esperarse una recuperación de 70-80 por ciento cuando no se trata de prematuros y de otras anomalías coexistentes.

2. Se relatan dos casos típicos de esta anomalía de nuestra serie de diez en 1956 con 60 por ciento de sobrevida.

RESUME

1. Depuis l'éminente contribution de Cameron Haight, en 1941, au taritement chirurgical de la fistule trachéoesophagienne et de l'atrésie oesophagienne, le tableau a changé. Alors qu'auparavant l'issue était presque invariablement fatale, on peut parler maintenant d'un taux élevé de survie chez les enfants traités chirurgicalement. La prématurité et les anomalies congénitales et associées sont des facteurs contre lesquels on ne peut rien dans cet état, mais ne sont pas en elles-mêmes un obstacle à une issue satisfaisante. C'est la nécessité pour les médecins et les personnes qui s'occupent des enfants, de reconnaitre cet état et d'établir un diagnostic précoce que souligne l'auteur. Si, après ce diagnostic précoce, une surveillance convenable, pré- et post-opératoire (comprenant une observation post-opératoire éloignée) est maintenue, on peut espérer un taux de guérison de 70 à 80% environ, à condition que les anomalies congénitales associées ne soient pas essentielles.

2. L'auteur rapporte ici deux types habituels de cette anomalie, d'après une série de 10 cas suivis en 1956, avec un taux de survie de 60%.

ZUSAMMENFASSUNG

1. Seit dem hervorragenden Beitrag von Cameron Haigh im Jahre 1941 über die chirurgische Behandlung der Luft-Speiseröhrenfistel und Epeiseröhren-Atresie hat das Bild eine Wandlung erfahren von einem fast unwandelbar tödlichen Ende zu einer hohen Überlebenszahl bei den chirurgischkorriegierten Säuglingen. Fehlende Reife und damit verbundene Anomalien sind nicht beherrschbare Faktoren dieses Zustandes, schliessen aber als solche nicht notwendig einen erfolgreichen Ausgang aus. Es ist das Erkennen des Zustandes durch Arzte und das Pflegepersonal und die frühzeitige Diagnosestellung, auf die Gewicht gelegt wird. Wenn nach frühzeitiger Diagnose eine geeignete prä- und post-operative Betreuung (einschliesslich späterer postoperativer Überwachung) gewährleistet ist, kann man eine Genesungsziffer von nahezu 70-80 Prozent erwarten, wobei fehlende Reife und begleitnd Anomalien nicht einbezogen sind.

2. Wiedergabe von 2 Typen dieser Anomalie aus unserer Series von 10 Fälien des Jahres 1956 mit 60 Prozent Überlebenden.

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Treatment of Pulmonary Tuberculosis with Cycloserine and Isoniazid: A Preliminary Report*

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Since the isolation by Harned[1] of Cycloserine, and reports by investigators that Cycloserine (CS) has wide but low antibacterial and antituberculous activity[2-4] many clinical trials have been and are being made. Favorable clinical results were initially reported[5-8] despite lack of success with CS therapy in tuberculous infected mice and guinea pigs.[9, 10] Despite the initial favorable reports with CS alone, the consensus has been that in doses (.25 gms. b.i.d. to q.i.d.) not calculated to produce excess toxicity, CS is not effective in pulmonary tuberculosis.[11-14] Resistance studies have shown a marked degree of bacterial resistance to CS after four to six months of therapy especially in re-treatment cases.[15] Schmidt[16] has shown the efficacy of combined therapy with CS-Isoniazid (INH) in infected Rhesus monkeys. Epstein et al[17, 18] have reported good results with the combination. Storey[19] has recently reported on 102 patients treated with CS-INH as compared to another group treated with INH-PAS. These reports were preliminary and the results were not definitive.

The following represents some observations on the treatment of far advanced and moderately advanced tuberculous patients with CS (.25 gms. b.i.d.) and INH (100 mgs. t.i.d.). The data was obtained from the first 12 INH-susceptible patients treated at this hospital. Eight of these cases never received anti-tuberculosis therapy in the past. Only two had received INH previously. One was included because of clinical response. The other had organisms initially susceptible to INH. Four of the 12 were colored. All were men. Their ages ranged from 26 to 62 years. All of the cases had one or more cavities. Six of them had poor, three had fair, and three had good results. Three of the four re-treatment cases had poor results. In light of subsequent studies it is probable that if the treatment in a few cases were continued for a longer time a better result might have been obtained. It appears that CS-INH therapy does not effect as rapid a radiological or bacteriological response as does INH-PAS therapy, and in particular, INH-Pyrazinamide (PZA) therapy.

Of the six poor result cases, four had radiological progression and two had minimal regression on x-ray film. All six were either persistently positive on smear and/or culture of sputum or reverted from negative to positive. Three of the six had a change in drug regimen because of poor response. The other three had operative intervention. All of the latter developed organisms with moderate to marked resistance to INH. Two remained INH-susceptible (their treatment was changed after one and two and one-half months of treatment) and one remained negative on culture.

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*From the Veterans Administration Hospital.

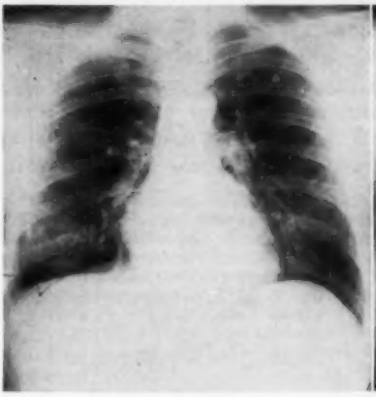

FIGURE 1

FIGURE 2

Figure 1 (Case 4, J. D.) (September 10, 1956) and *Figure 2* (Case 4, J. D.) (March 20, 1957): After moderate initial improvement cavity became larger in right lower lobe after six months of therapy. Sputum remained positive. Susceptibility studies four months after onset of treatment showed resistance to INH.

The following is a brief summary of a poor response case:

Case 4: J. D., a 38 year old white man, had CS-INH therapy begun September 19, 1956. He previously had a coin lesion excised from the right lower lobe on June 4, 1956 and was discharged June 22, 1956. In retrospect this was probably tuberculous in origin. On admission there was an infiltrate with an area of rarefaction at the right base. After one month of therapy with CS-INH there was moderate decrease in the size of cavity in the right lower lobe. This subsequently became stationary. Five months thereafter there was progression of disease in this area (Figures 1 and 2). Sputum smears and cultures remained positive. He had right lower lobectomy six months after the start of treatment. CS was stopped two weeks prior to the operation and streptoduocin and PAS were added to the INH therapy. Subsequent to lobectomy he had an uneventful recovery. Cultures were INH—susceptible from September to November, 1956, and moderately resistant to INH between January and March, 1957.

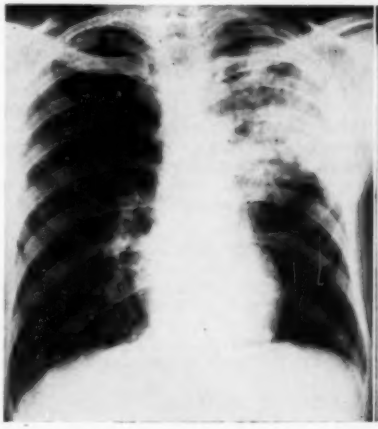

FIGURE 3

FIGURE 4

Figure 3 (Case 7, J. M.) (October 16, 1956) and *Figure 4* (Case 7, J. M.) (April 17, 1957): There was moderate decrease in exudative component in the infiltrate left upper lung field. Cavity persisted after six months of therapy with CS-INH. Lobectomy performed May 14, 1957.

Three cases were considered initially to have fair results. Two of them had negative sputum after three months. It should be noted that although these patients were considered fair in their initial bacteriological and radiological response, in all of the cases a cavity persisted for at least six months. In one case operative intervention was eventually necessary and in another there was progressive disease three months after stopping a five month course of CS-INH. A representative case is the following:

Case 7: J. M., a 34 year old white man, had caseo-cavernous disease in the upper half of the left lung field. CS-INH therapy was begun October 25, 1956. After two months of treatment smear became negative and after three months of treatment cultures were negative. The cavity, although smaller, persisted in the left upper lobe at the end of six months (Figures 3 and 4). Because of this, lobectomy was performed on May 14, 1957. On x-ray June 1, 1957, a focus previously present in the superior segment of the left lower lobe was noted to have excavated despite continued INH-CS and this was resected on August 2, 1957, after addition of SM-PAS. Following a space-filling thoracoplasty on September 12, 1957, he had an uneventful recovery.

Cycloserine blood levels were obtained weekly on all patients. The blood levels ranged from 8 to 18 micrograms per milliliter. The majority had a range of between 8 and 12 micrograms. The value for each patient seemed fairly constant. No appreciable electroencephalographic abnormality was noted. In only one case was treatment stopped because of psychological manifestations or electroencephalographic findings. In two definite personality changes were noted. The patients appeared euphoric and were somewhat shallow in their conversation. One was noted to talk in his sleep.

In reviewing this small number of cases, it is felt that results with INH, 300 mgs. and CS, 0.5 gm. daily, are relatively poor. It is our impression that this combination is inferior to other modes of combined therapy. An interesting finding has been that th of the poor result cases, all of whom eventually went to surgery, had initially full sensitivity to INH. Within a short time (one to four months of therapy) their bacilli became moderately resistant to INH. Apparently CS in the dosage used did not delay the appearance of INH-resistance in these cases. There was no adequate CS-susceptibility study available.

SUMMARY

Results of combined therapy with cycloserine, 0.5 gm., and isoniazed, 300 mgs. daily, in the first 12 cases treated have been generally unfavorable. In cases that respond favorably it appears that the bacteriological and radiological response is slower than with combinations of streptomycin, aminosalicylic acid and isoniazid. Failure of cycloserine to delay the emergence of isoniazid resistant organisms was noted in three of these cases.

RESUMEN

Los resultados de la terapéutica combinada con cicloserina 0.5 mg. e isoniacida (300 mg.) diariamente en los primeros 12 casos, han sido generalmente desfavorables. En los que respondieron favorablemente parece que la respuesta bacteriológica y radiológica es más lenta que en las combinaciones de estreptomicina, PAS e isoniacida. El fracaso de la cicloserina para retardar la aparición de la resistencia a la isoniacida, se notó en tres de los casos.

RESUME

Les résultats de la thérapeutique associant la cyclosérine, 0,5 mmg. et l'isoniazide à la dose de 300 mmg. par jour, dans les premiers douze mois de traitement, ont été généralement défavorables. Dans les cas qui répondent favorablement, il semble que la réponse bactériologique et radiologique est pius lente qu'avec les combinaisons de streptomycine, de P.A.S. et d'isoniazide. L'échec de l'action de la cyclosérine pour retarder l'apparition de bacilles résistants à l'isoniazide fut noté dans trois de ces cas.

ZUSAMMENFASSUNG

Die Ergebnisse der ersten 12 mit einer kombinierten Therapie Cycloserin 0,5 mg und INH 300 mg täglich behandelten Fälle waren im ganzen unbefriedigend. In den Fällen, die günstig reagierten, scheint es, dass die bakteriologische und röntgenologische Reaktion langsamer erfolgt als bei Kombinationen von Streptomycin, PAS und INH. Bemerkt wurde ein Versagen von Cycloserin hinsichtlich einer verzögernden Wirkung beim Auftreten von INH-resistenten Keimen in 3 von diesen Fällen.

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Unsuspected Bronchogenic Carcinoma*

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Unsuspected Bronchogenic Carcinoma

Reported here is an analysis of 32 cases of bronchogenic carcinoma treated for various diseases in which the correct diagnosis was never seriously considered before death. Thus, during the past 10 years the correct diagnosis has not been suspected in 5 per cent of the 650 cases of primary carcinoma of the lung treated on this Thoracic Surgery Section. Kennedy Hospital's 150,000 admissions had a proved bronchogenic carcinoma incidence of 4 per thousand. Histologic proof of diagnosis while undergoing treatment was obtained in 91 per cent of cases by either biopsy or resection. Some patients had obvious clinical cancer and were given some form of therapy, but histological proof of the diagnosis was established only by autopsy. A few patients were treated for cancer on the basis of clinical findings, but tissue diagnosis was never obtained. These cases are not included in our lung cancer register.

The *presenting complaints* of patients with unsuspected lung cancer were extremely variable (Fig. 1). So impressive has this been that bronchogenic carcinoma appears to have replaced syphilis as the great masquerader. Joint pain (48 per cent) was the most common single presenting complaint, usually involving the shoulder, low back or hip. Neurological symptoms (coma, sphasia, hemiparesis, paraplegia or facial nerve paralysis) were present in 13 of these 32 patients. Gastrointestinal symptoms were present

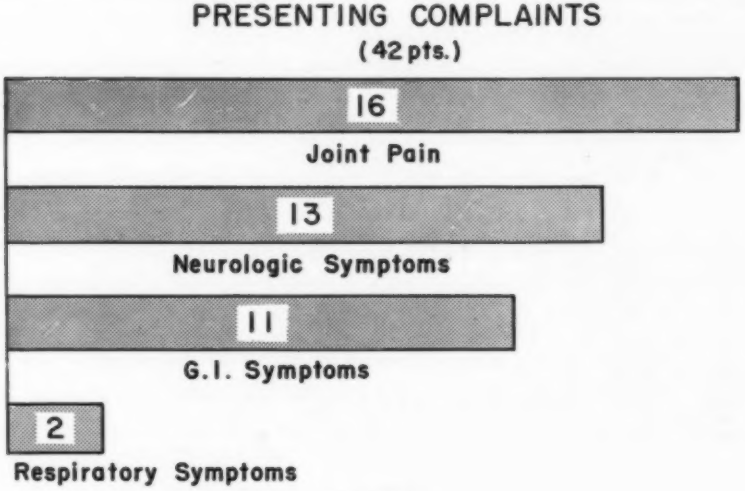

FIGURE 1

*From the Thoracic Surgical Section, Veterans Administration Hospital.
Presented before the Annual Meeting of the Southern Chapter, American College of Chest Physicians, Miami, Florida, 1958.

in 11. Only two, both with dyspnea and fever, gave presenting complaints arising primarily from the respiratory system. There was a history of bronchitis or asthma for many years in 20 per cent of the cases. Two were admitted following falls, one resulting in paraplegia, the other in knee pain. Most of the 32 had had one or more previous admissions which offered opportunity for diagnostic study, had the possibility of bronchogenic carcinoma been entertained.

Physical findings were usually not suggestive of pulmonary cancer. Some chest abnormality on physical examination was found in only eight. One was thought to have typical acute lobar pneumonia and Type 17 pneumococcus was isolated from the sputum. There was neurological deficits in 13 patients, slightly more than half of these were due to cord compression. Two had paralysis of the facial nerve. Three had craniotomy for brain tumors. Another was diagnosed as having typical cardiovascular accident.

Completely negative *routine chest x-ray films* were obtained from six patients (Fig. 2). A soft infiltrate interpreted as tuberculosis or pneumonitis was the roentgenographic finding in 13, and five of these shadows cleared during hospitalization. Bullous emphysema, usually bilateral, with no apparent density, was found in five roentgenographic studies. Three patients had hilar prominences; two had well-defined cavities in the upper lobes and two had atelectasis. One showed an aneurysm of the aorta and another pleural effusion which occurred with proved pulmonary and pericardial tuberculosis. Osteolytic lesions of the spine were demonstrated in eight. All areas of the spine seemed to be about equally involved.

In the three who had bronchoscopy, no abnormality was found. The most common *clinical diagnosis* was tuberculosis, 15 of the patients having had either proved or suspected tuberculosis and 10 having had positive sputa for acid fast bacilli on the last hospital admission. In one of these,

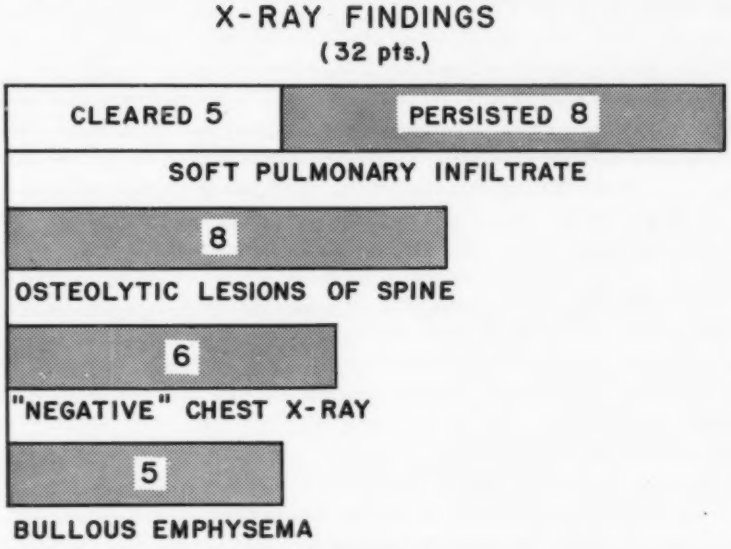

FIGURE 2

no evidence of tuberculosis was found at autopsy. Five of the cases were diagnosed as spinal cord tumors.

Five were under 35 years of age, but the mean age was 53 years. Twenty of the tumors were anaplastic carcinoma; six were squamous and six were adenocarcinoma.

From onset of symptoms to death the time varied from one day for a patient with massive gastrointestinal hemorrhage to five years in one with carcinoma and far-advanced pulmonary tuberculosis who died from coronary occlusion. The mean survival time was 8.1 months from onset of symptoms to death, with no patients living after five years compared with our resected cases, which had a five-year "cure" rate of 31 per cent.

Half of the tumors occurred in the right upper lobe. There was involvement of the liver in half of all cases. The brain was involved in eight; bone in 13, adrenal in 13; the heart, spleen, gastrointestinal tract, kidney, thyroid and skin were involved in one or more cases. There was no difference in site or incidence of metastasis between the various histologic types of tumors.

It would appear that the frequency of missed diagnoses would fall as we gain more experience and see more cases. This is not the case. A third of these errors were made last year. One of the tumors was so elusive that although there were metastases to skull, spine, liver and supraclavicular nodes, the primary tumor in an area of pneumonia was not even noticed on gross examination at autopsy.

Two patients, who died of pneumonia and mesenteric thrombosis, had well-localized tumors without metastasis which could otherwise have been easily removed at surgery with a reasonable probability of cure.

Seventy-five per cent of these patients had either pulmonary tuberculosis or neurological symptoms. Bronchogenic carcinoma metastasizes to the brain in about 25 to 50 per cent of reported cases. The overall picture shows that from 16 to 38 per cent[1] of metastatic brain tumors are bronchogenic in origin. However, it seems that bronchogenic carcinoma is the most common primary site of metastatic brain lesions in males over 35 years of age. In a given case with a brain tumor and pulmonary infiltrate the chances are about even that bronchogenic carcinoma is the correct diagnosis. Patients with tuberculosis or emphysema may have an increase in the incidence of cancer over patients with a normal respiratory system.

We would recommend that any patient with signs and symptoms of spinal or brain compression have at least a posterioanterior and both oblique x-ray films of the chest and multiple sputa specimens studied cytologically. If any of these studies are in the least abnormal (including areas of emphysema) more complete pulmonary studies, including bronchoscopy and planigrams, should be done to rule out bronchogenic carcinoma.

We are convinced that any man with joint pain of unknown etiology, particularly if multiple and involving the shoulders, back or hip, should have an adequate study of his lungs to rule out cancer.

Elderly male smokers with longstanding pulmonary tuberculosis should be studied carefully from time to time ascertain the development of cancer.

SUMMARY

1. This is a report of 32 cases of bronchogenic carcinoma in which the correct diagnosis was never seriously considered before death. These errors occurred in 650 cases of bronchogenic carcinoma from among about 150,000 admissions.

2. The presenting complaints were extremely variable. Joint pain, neurological and gastrointestinal symptoms were present in most cases. Respiratory symptoms were the presenting complaints in only two.

3. Physical findings revealed neurological deficits in 13 and eight had abnormality on examination of the chest.

4. Negative chest x-ray films were obtained from six. Soft infiltrations suggestive of tuberculosis or pneumonia were present in 13; five of these shadows disappeared during hospitalization. Bullous emphysema was the next most common finding on x-ray film.

5. Half of the patients were considered to have tuberculosis and about a third had positive sputa.

6. Metastases were usually extensive, involving the liver, adrenal, bone, brain, heart, spleen, gastrointestinal tract, kidney, thyroid and skin.

7. Study of these errors in diagnosis indicates that spinal or brain compression, joint pain and pulmonary tuberculosis should make one cognizant of the possibility of coexisting bronchogenic carcinoma and that careful, repeated examinations should be made in patients with these conditions to prove or disprove the presence of cancer.

RESUMEN

1. Se refieren 32 casos de carcinoma bronquigénico en los que el diagnóstico correcto nunca se consideró con seriedad antes de la muerte. Estos errores ocurrieron en 650 casos de carcinoma bronquiogénico entre 150,000 ingresos.

2. Los síntomas que hubo fueron muy variables. Dolor articular, síntomas neurológicos y gastrointestinales en la mayoría de los casos. Sólo en dos hubo síntomas respiratorios.

3. Los hallazgos físicos revelaron déficits neurológicos en 13 y ocho tenían anormalidades al examen del tórax.

4. Se obtuvieron películas negativas en seis. Infiltraciones blandas sugerentes de tuberculosis o neumonía en 13; cinco de estas sombras desaparecieron durante la hospitalización. El hallazgo más frecuente enseguida fué enfisema buloso a los rayos X.

5. La mitad de los enfermos se creyó que eran tuberculosos y alrededor de un tercio tuvieron esputos positivos.

6. Las metástasis fueron generalmente extensas, comprometiendo el hígado, las suprarrenales, huesos, cerebro, corazón, bazo conducto gastrintestinal, riñón, tiroides y piel.

7. El estudio de estos errores en el diagnóstico indica que la compresión espinal o cerebral, el dolor articular y la tuberculosis pulmonar deben hacer que uno reconozca la posibilidad de carcinoma bronquiogénico coexistente y de que deben hacerse exámenes cuidadosos y repetidos en enfermos con estos padecimientos para demostrar la existencia o no de cancer.

RESUME

1. Les auteurs présentent une communication portant sur 32 cas de cancer bronchique dans lesquels le diagnostic correct ne fut jamais sérieusement considéré avant la mort. Ces erreurs survinrent dans 650 cas de cancer bronchique pour un total d'environ 150.000 admissions.

2. Les symptômes présentés furent extrêmement variables. Des douleurs articulaires, des symptômes neurologiques et gastro-intestinaux existaient dans la plupart des cas. Ce n'est que dans deux cas que les malades se plaignaient de symptômes respiratoires.

3. A l'examen physique on constata dans 13 cas des signes de déficit neurologique et huit présentaient une anomalie à l'examen du thorax.

4. Les films thoraciques ne montrèrent aucune anomalie chez 6 malades. It existait de légères infiltrations, évocatrices de tuberculose ou de pneumonie dans 13 cas; cinq de ces ombres disparurent pendant l'hospitalisation. L'emphysème bulleux fut ensuite la constatation la plus fréquente sur les films radiologiques.

5. La moité des malades furent considérés comme ayant une tuberculose et environ un tiers avaient des expectorations positives.

6. Les métastases furent habituellement extensives, atteignant le foie, les capsules surrénales, les os, le cerveau, le coeur, la rate, l'appareil digestif, le rein, la glande thyroïde et la peau.

7. L'étude de ces erreurs de diagnostic indique que la compression de la moelle épinière ou du cerveau, les douleurs articulaires et la tuberculose pulmonaire devraient avertir le praticien de la possibilité d'un cancer bronchiques coexistant. Des examens soigneux et répéts devraient être faits chez de tels malades pour permettre de prouver ou non la présence d'un cancer.

ZUSAMMENFASSUNG

1. Es handelt sich um einen Bericht über 32 Fälle von bronchogenem Carcinom, bei denen die richtige Diagnose in keinem Fall ernstlich in Erwägung gezogen wurde vor dem Tode. Ein solcher Irrtum kam vor unter 650 Fällen von Bronchuscarzinom bei ungefähr 150 000 Einweisungen.

2. Die bestehenden Beschwerden waren äusserst verschieden Gelenkschmerzen, neurologische und gastrointestinale Symptome bestanden in den meisten Fällen. Symptome von seiten des Respirationstraktes waren nur 2 mal die vorgebrachte Beschwerde.

3. Physikalische Befunde wiesen 13 mal neurologische Mängel auf, und 8 Kranke hatten Veränderungen bei der Thoraxuntersuchung.

4. Negative Thoraxröntgenaufnahmen wurden in 6 Fällen gewonnen. Auf Tuberkulose oder Pneumonie verdächtige weiche Infiltrationen lagen 13 mal vor; 5 von diesen Schatten bildeten sich während des Krankenhausaufenthaltes zurück. Ein bullöses Emphysem war der nächsthäufige Befund bei der Lungenröntgenaufnahme.

5. Von der Hälfte der Kranken wurde angenommen, dass sie eine Tuberkulose hatten und ungefähr ein Drittel hatte positives Sputum.

6. Gewöhnlich waren die Metastasen ausgedehnt und betrafen Leber, Nebenniere, Knochen, Gehirn, Herz, Milz, Magen-Darmkanal, Niere, Schilddrüse und Haut.

7. Die Analyse einer irrtümlichen Diagnose kennzeichnet, dass eine spinale oder cerebrale Kompression, Gelenkschmerzen und Lungentuberkulose an die Möglichkeit eines gleichzeitig bestehenden Bronchuscarzinomes denken lassen sollen, und dass sorgfältig und wiederholt untersucht werden muss bei Kranken mit solchen Erscheinungen, um das Bestehen eines Krebses zu beweisen oder auszuschliessen.

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Chromogenic Acid-fast Mycobacteria in Cavernous Lung Lesions

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Since 1918, when Corper made the observation that acid-fast bacilli cultured from the sputum of two patients suffering from cavernous tuberculosis, did not cause typical tuberculous lesions in guinea-pigs, similar cases have been observed in large numbers. Recently several publications described cases of changes of the lungs, glands, urogenital system, and cerebral meninges which clinically and roentgenologically had been diagnosed as tuberculosis, but were caused by atypical chromogenic, acid-fast bacteria. In most cases tuberculine test was positive. Tuberculostatic treatment was, in almost all cases, without influence. Bacteria were partly chromogenic, partly they formed yellow and orange pigment in the dark, they grew unusually fast on usual culture medium. They grew also on agar and bouillon. The strains developed more slowly in room temperature than in the incubator, were catalase-active, urease moderately positive and gave a negative neutral-red reaction. Frequently resistance against usual tuberculostatics especially INH, was observed. Animal experiments revealed striking results. Guinea-pigs, rabbits and young chicken, as well as rhesus-monkeys were seldom infected and the course of the disease never was fatal. Only intraveneous injections to mice, rats and marmots caused pathologic changes of tuberculous character and the animals died. It must be stressed that subcutaneous injections of normal BCG strains in marmots caused lethal Tbc-infections, since these animals have a special susceptibility to foreign toxines, bacteria and putridity-amines. All animals infected with the bacterium forming yellow pigment had a positive tuberculine reaction.

The above summarized results of investigations are from Pollack and Buhler, Wood, Someya and Hayashi, Runyon, Young, Wilson and Morton, Tarshis et al., Yegian et al., Morse et al., Florence and from the team of Steenken Jr.

Our own observations are based on four cases:

Case 1: E. S., born March 17, 1916, had tuberculosis in the right lung in 1948 with pneumothorax, thoracocaustic. In 1950 there was a cavity in the left upper lobe not benefited by pneumothorax, thoracocaustic and intense chemotherapy with 50 g. streptomycin, 1500 g. PAS, 14,4 g. Conteben, 50 g. INH, and 35 g. Flavoteben. The pneumothorax on the right side was abandaned. In 1952 drainage of the cavity on the left and resection of the first and second anterior-ribs (Figure 1) was without benefit. In January 1954 pneumectomy of left lung. Ten months later death resulted from pneumonia.

The specimen revealed a large cavity in the left upper lobe with irregular walls. The rest of the lung tissue was either emphysematous or collapsed and indurated, and penetrated by node like infiltrations. Smaller foci also were present in the lower lobe. Microscopic sections Figure 2: Caseous tissue was found besides foreign body giant cells, caused by preoperative inhalations of antibiotics.

Bacteriological findings: 1953 resistance against INH and thiosemicarbazone. These bacteria, also growing on agar, formed chromogenic, yellow or orange strains and were not pathogenic for guinea-pigs. From five different foci of the operation specimen bacteria with different susceptibility for drugs were cultured. The results corresponded to those of 1953.

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Case 2: F. H. born November 12, 1916. In 1951 had tuberculosis of the right lung with cavity. Pneumoperitoneum with pneumothorax and phrenemphraxis. Also had bronchial stenosis on the left side. In 1953 a large cavity developed in the left upper lobe. In January 1954, while pneumothorax was present on the right, left upper lobectomy was done. Up to this time, large quantities of Streptomycin, PAS, INH, had been given. Death occurred January 6, 1957.

The resected specimen revealed induration of the left upper lobe, scars and alveolar collapse with anthracotic pigment. The cavity was 3 x 1 x 1 cm. and was lined with epithelium. In the vicinity there were specific round foci with caseous centers and bronchial tuberculosis (Figure 3).

Bacteriological findings: Strains of orange-yellow mycobacteria from sputum and operation-specimen, which were avirulent in guinea-pigs. Typical growth on tuberculosis culture medium, agar and blood agar which occurred at room temperature within three or four days.

Case 3: K. Z. born April 4, 1893. In 1951 had weakness, sputum and cough. In 1952 had fever with same symptoms. X-ray film revealed two round foci with central

FIGURE 1

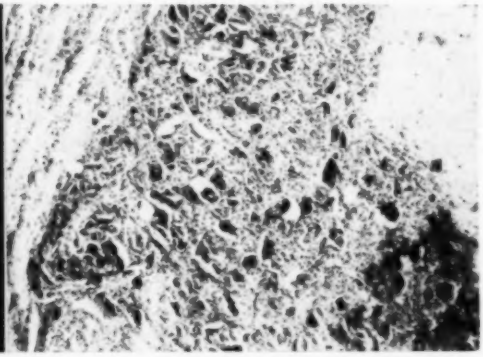

FIGURE 2

Figure 1: Pat. E. S. Nov. 16, 1953 (see text).—*Figure 2:* Pat. E. S. Caseous tissue besides foreign body giant cells and crystals caused by preoperative inhalations of antibiotics.

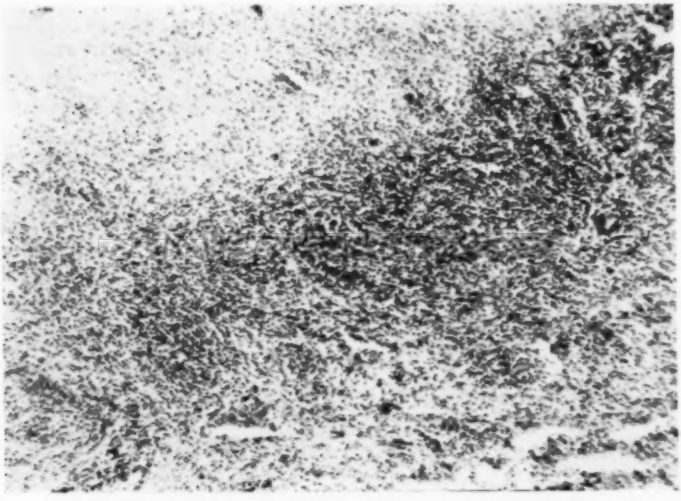

FIGURE 3: Pat. F. H. Typical caseous tissue.

cavities besides fibrous tuberculous lesions of the right upper lobe Figure 4. Intense therapy with INH. Lesions became fibrous. Rather good general status up to the present time. Sputum still positive.

Bacteriological findings: Strains of orange pigment forming mycobacteria, growing on Hohn cuture medium. Inoculation in guinea-pigs caused swelling of lymph nodes, which decreased quickly. Animals survived more than a year. Microscopical findings after death: No pathologic changes. In the course of further animal passages the bacteria developed and more evidence of atypical mycobacterium tuberculosis. These cultures did not reveal the usual picture of normal bacteria. Bacteria cultured from one single animal, being chromogenic and acid-fast, were not virulent after inoculation in another animal.

Case 4: A. L., born September 2, 1930. In 1948 had bilateral tuberculosis with cavities. Treatment: Pneumothorax left side, Conteben Figure 5. In 1954 had acerbation on left side, pneumothorax was abandoned. She had 48 g. INH, 1000 g. PAS. In 1952 in an other sanatorium extrapleural pneumothorax was done on right side with streptomycin administration.

In 1955 exacerbation in the medial field of the left lung. Resistance: Streptomycin 1 g., PAS 0,1 g., INH 0,01 g. Therefore again treatment with INH 50, og. Viomycin 60, og. and PAS infusion i.v. 650 g. Positive results concerning the left side lesions. Resistance of bacteria in 1957 with the same results. Extrapleural pneumothorax right side was abandoned in 1957.

In 1956 bacteria had been cultured from sputum which formed yellow pigment and revealed the same characteristics in animal passages and in culture medium as described above.

If compared with literature, in all cases tuberculosis had been diagnosed clinically and by X-ray. Positive tuberculine tests, the clinical data, the X-ray series, the course of the disease and microscopical sputum findings were significant. In case 2 the anatomist gave the diagnosis in his microscopical findings. But we had isolated chromogenic, acid-fast bacteria from culture.

The question has to be discussed, whether the bacteria had been chromogenic bacteria from the very beginning, or had been real tuberculosis bacteria which developed into chromogenic acid-fast bacteria.

FIGURE 4: Pat. K. Z. March 15, 1952 (see text).

The first assumption is easy to understand but cannot be proven. The frequent bacteriological examinations during the course of the disease should have led to findings of chromogenic bacteria at an earlier stage. That this did not happen is an argument for the proof, that a genuine tuberculosis was the first disease. The chromogenic mycobacteria may originate from the old "burned-out" tuberculosis (Wolinsky) or result from a mutation and selection among the old strains. We are inclined to assume the last point. It was not succeeded to recultivate genuine mycobacteria tbc. from chromogenic bacteria. A further stress to the assumption of a mutation is the fact, that susceptibility of tuberculostatics was different during the period of observation. Mutation is directed against susceptibility of tuberculosis. These changes may also influence the color, form and pathogenity and thus cause the changes observed.

A further point to underline "mutation" is the fact, that histological findings were the same in both cases, mycobacterium tuberculosis and chromogenic bacteria. Massive tuberculostatic therapy causes mutation more frequently than a moderate therapy. This does not exclude, that mutation also occurs before tuberculostatic therapy, as emphasized by several authors. However, the frequency of findings of mutation during the period of tuberculostatic therapy is a confirmation of the thought, that *one* factor is necessary to provoke mutation.

There is no doubt, that all possibilities quoted have a mere hypothetic value. The increasing number of observations of chromogenic bacteria, however, forces us to search this problem thoroughly, always considering the area of tuberculostatics. This paper has not the intention to answer, but to discuss and to deal with this problem.

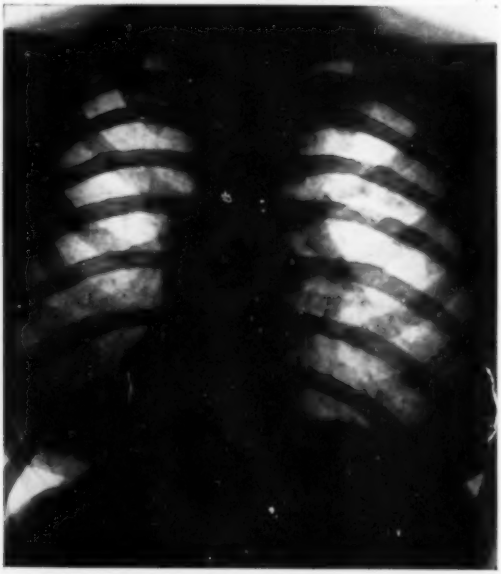

FIGURE 5: Pat. A. L. June 6, 1951 (see text).

SUMMARY

A comparison is made of atypical acid-fast chromogenic microbacterium obtained from sputum and surgical specimens of four patients with similar findings in the English-American literature. It is believed that the bacteria are the same. The tuberculin test is positive and lesions are histologically similar to lesions created by mycobacterium tuberculosis of the human type; since on previous occasions on those patients tubercle bacilli were isolated, it is assumed that in our cases the atypical mycobacterium represent mutation of tubercle bacilli. Such mutations were found also before tuberculosis therapy; however, they seem to be more frequent now and gain differential diagnostic importance.

RESUMEN

Se comparan las microbacterias atípicas, ácido-resistentes cromógenas obtenidas de esputos y de especímenes quirúrgicos de cuatro enfermos con hallazgos semejantes en la literatura Anglo-americana.

Se cree las bacterias son las mismas.

La reacción tuberculínica es la misma y las lesiones histológicas son similares a las lesiones producidas por la variedad humana del microbacterium tuberculosis; puesto que antes, en los mismos enfermos se aislaron bacilo de la tuberculosis es de pensarse se que estos bacilos atípicos son mutaciones del bacilo de la tuberculosis.

Tales mutaciones se encuentran a veces según las estadísticas de tuberculosis; sin embargo parecen ahora ser más frecuentes y están teniendo más importancia en el diagnóstico diferencial.

RESUME

L'auteur compare les germes acido-résistants chromogènes atypiques prélevés dans l'expectoration et les pièces chirurgicales de 4 malades, avec les constatations semblables qui ont été publiées dans la littérature anglo-américaine. Il pense que les germes sont les mêmes. Le test tuberculinique est positif, et les lésions sont histologiquement semblables aux lésions créées par le mycobacterium tuberculosis de souche humaine; comme antérieurement, un bacille tuberculeux a été isolé chez ces mêmes malades, l'auteur pense que dans ses cas le mycobacterium atypique reprèsente une mutation de bacille tuberculeux. De telles mutations furent découvertes au moment des études statistiques sur la tuberculose; cependans, elles semblent être plus fréquentes maintenant et prendre plus d'importance dans le diagnostic différentiel.

ZUSAMMENFASSUNG

Atypische, säurefeste, chromogene Mycobakterien, die aus Sputum und Operationpräparaten von 4 Patienten isoliert werden konnten, werden mit ähnlichen Befunden aus dem anglo-amerikanischen Schrifttum verglichen. Es dürfte sich um die gleichen Erreger handeln. Da die Tuberkulinprobe positiv ausfällt, die Läsionen histologisch denen gleichen, die durch das Mycobact. tuberculosis var hom. hervorgerufen werden und da schliesslich früher bei den Patienten echte Tuberkelbakterien gezüchtet werden konnten, wird angenommen, dass es sich bei den atypischen Mycobakterien in unseren Fällen um mutativ geänderte Tuberkelbakterien

handelt. Derartige Mutationen kamen auch in der Ära vor den Tuberculostaticis vor, treten aber offensichtlich jetzt häufiger auf und sind deshalb auch differentialdiagnostisch zu beachten.

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Should a Chronic Atelectatic Lung Be Reaerated or Excised?*

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Chronic collapse of an entire lung frequently results from bronchostenosis of traumatic,[1-21] congenital or tuberculous origin. Prior to 1949, patients with chronic atelectasis were often treated either by pulmonary resection[11, 12, 13] or by the institution of pneumothorax to correct the mediastinal displacement.[8, 10] Griffith,[14] in 1949, first described reinflation of a collapsed lung after seven months by resection of the stenotic segment of bronchus. There have been subsequent similar reports of reaeration of lungs which had been atelectatic for six weeks to 14 years.[15-21]

Clinicopathologic studies performed on lungs which had been collapsed five weeks to 26 years due to complete stenosis of the mainstem bronchus failed to reveal any gross or microscopic evidence of infection or morphologic change which might be incompatible with re-establishment of respiratory function.[11-13, 22] Experimental studies on dog lungs which had been atelectatic up to 17 months also demonstrated no histologic alterations.[23, 24]

In spite of relatively frequent recent reports of re-expansion of chronically collapsed lungs, there have been strikingly few physiologic studies on these patients following such reinflations that would indicate that chronic atelectasis is a physiologically reversible process. The only previous experimental study of the physiologic effects of reaeration of a chronically atelectatic lung was made by Webb and Burford.[22] Their conclusion, based on studies of three dogs after atelectasis of three and one-half to seven months' duration, was that blood flow and oxygenation through the reinflated lung are normal.

Our interest in this subject was stimulated by a recent case report of Mahaffey, Creech, Boren and DeBakey[21] in which bronchoplasty and reinflation of atelectatic lung 11 years after traumatic bronchostenosis resulted in a decrease in the patient's peripheral arterial oxygen saturation with evidence of approximately 37 per cent right-to-left shunt five months postoperatively.

If chronic atelectasis can be shown to be physiologically reversible, bronchoplasty and reinflation is naturally the treatment of choice. However, if such a process is not reversible, then reaeration of the atelectatic lung may actually be harmful to the patient, for it has been shown that an expanded non-functioning lung is a greater physiologic deficit than a collapsed lung.[25, 26] Accordingly, the following series of experiments

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were undertaken in order to gain additional information as to whether chronically atelectatic lung should be resected or reinflated.

Methods

Atelectasis of the entire left lung was produced in 15 mongrel dogs by the transbronchoscopic application of 35 per cent silver nitrate solution circumferentially to the mucosa of the left mainstem bronchus.[27] One or two applications usually sufficed to produce the desired complete stenosis 10 to 14 days after cautery.

The diagnosis of atelectasis was made by physical examination, bronchoscopy, roentgenograms and bronchograms. A typical roentgenogram showed shift of the mediastinum to the atelectatic side (Fig. 1). The diagnosis was later confirmed at thoracotomy.

The physiologic deficit produced by the atelectasis was evaluated by means of a graph relating arterial oxygen saturation to alveolar oxygen tension as described by Perkins *et al.*[28] Arterial oxygen saturations were determined by means of a modified Wood continuous recording cuvette oximeter which had been calibrated with Van Slyke-Neill determinations. Blood from the femoral or carotid artery was circulated through the cuvette and returned to a convenient vein, clotting being prevented by the administration of heparin. End expiratory samples approximating the composition of alveolar air were obtained with a Rahn valve, and analyzed by Pauling-Beckman model C oxygen analyzers. Mixed venous blood was obtained from a cardiac catheter fluoroscopically positioned in the pulmonary artery or right ventricle.

The vessels used for the cuvette, and the jugular vein used in introducing the cardiac catheter were exposed using procaine infiltration anesthesia In this way, it was possible to determine the peripheral arterial saturation and mixed venous saturation with the animal awake and unsedated, breathing room air.

FIGURE 1, Dog 189: Normal chest x-ray on September 14, 1956. Left mainstem bronchus cauterized on September 14, 1956 and September 25, 1956. Bronchoscopy on October 8, 1956, revealed complete stenosis of the left mainstem bronchus.

Bronchogram on March 25, 1957, shows marked shift of the heart and mediastinum to the left with complete atelectasis of the left lung. The stenotic stump of the left mainstem bronchus is well outlined with contrast material.

Resection of the stenotic portion of the left mainstem bronchus with end-to-end anastomosis was performed on April 1, 1957.

Bronchogram on May 24, 1957, reveals the left lung fully reaerated and left bronchial tree well outlined by contrast material.

Anesthesia was then induced using 12-17 mg./Kg. of intravenous pentothal. While administering this it was possible to monitor the saturation with the oximeter, thereby making certain that it was maintained at the preanesthetic levels. A saturation-tension curve was then determined by allowing the animal to breath varying mixtures of nitrogen, air and oxygen prepared in a Tissot spirometer. In this manner the alveolar oxygen tension was varied from 50 to 670 mm. Hg.

The fraction of right to left shunting: *i.e.*, the percentage of total cardiac output passing through the atelectatic lung, was calculated by the standard mixing equation expressed in terms of per cent saturation, neglecting small amounts of dissolved oxygen. Expressed in standard terminology, the equation is: $Qva/Qt = (S^{c}O_2\text{-}SaO_2)/(S^{c}O_2\text{-}SvO_2)$, where Qva/Qt = fraction of cardiac output shunted, (x 100 = percentage of shunting), $S^{c}O_2$, SaO_2, SvO_2, represents oxygen saturations of lung capillary blood, arterial blood, and mixed venous blood respectively. Normal oxygen saturation of lung capillary blood is assumed to be 97 per cent when the animal is breathing room air.

Within one to two weeks following the above-described studies, thoracotomy was performed, and the left lung was found shrunken to less than ¼ normal size with the color and consistency of normal liver. The stenotic portion of the left mainstem bronchus was resected, and anastomosis was performed with 00000 silk using a continuous everting mattress technique interrupted four times about the circumference of the bronchus. A series of experiments in this laboratory, as well as studies by Jackson *et al.*,[29] showed the everting method of suturing to be one of the most satisfactory for bronchial anastomosis. Upon opening the bronchus of the atelectatic lung, a pale viscoid mucus was constantly encountered and then aspirated as completely as possible. The lung expanded easily in all cases where satisfactory anastomosis was possible.

Ten days to six weeks after bronchoplasty peripheral arterial satura-

TABLE I—CHRONIC ATELECTASIS ENTIRE LEFT LUNG
(Animal Awake)

Dog	Duration In Weeks	Peripheral Arterial Sat.	Mixed Venous Saturation	Per Cent Shunt
296	2½	90	49	12
998	3½	87	59	26
271	5	86	58	28
34*	7	82	54	33
961	7	95	58	5
297	11	86	47	22
589	15	95	67	7
309	15	93	54	9
113	15	95	57	5
939	19	94	75	14
189	19	91	58	15
333	20	99	54	0
278	26	95	54	5
822	27	88	57	22
124	32	87	47	20

*Atelectasis plus left pneumothorax.

TABLE H—CHRONIC ATELECTASIS ENTIRE LEFT LUNG
(Results of Bronchoplasty)

Dog	Duration of Atelectasis (Weeks)	Per Cent Shunt	
		Atelectasis	Reinflation
296	2½	12	0
998	3½	26	6
34*	7	33	0
961	7	5	0
309	15	9	0
939	15	14	4
189	19	15	0
822	27	22	0
124	32	20	2

*Atelectasis plus left pneumothorax.

tion, mixed venous saturation and a saturation and a saturation-tensions curve were again determined by the methods described previously.

Results

Control studies were done on seven normal animals before producing atelectasis, and normal curves lying close to the *in vitro* oxyhemoglobin dissociation curve were obtained as previously described.[28] Hence control studies were not carried out in all animals.

Fifteen dogs with atelectasis of the entire left lung of two and one-half- to 32-weeks' duration were studied, and the physiologic deficit expressed in terms of percentage of the cardiac output passing through the atelectatic lung. These results are summarized in Table I.

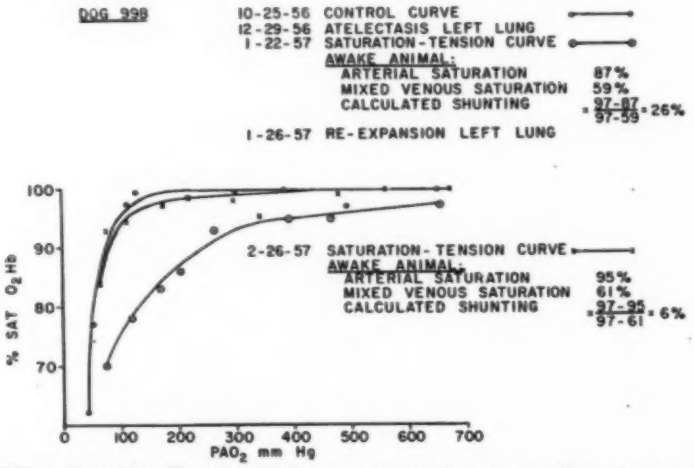

FIGURE 2, Dog 998: The "control" saturation-tension curve obtained prior to the production of atelectasis closely approximates the *in vitro* oxyhemoglobin dissociation curve for the blood of dogs.

The lowermost curve was determined three and one-half weeks after the development of atelectasis. The depression and linearly rising slope are characteristic of anatomical right to left shunting.

The intermediate curve obtained one month after reinflation of the atelectatic lung approaches the "control" curve, signifying a marked reduction of right to left shunting.

Shunting in the 14 dogs with uncomplicated atelectasis of the entire left lung varied from zero to 28 per cent with an average value of 14 per cent. In two of the animals, Dogs 998 and 822, the determinations were confirmed within the limits of accuracy of the method.

Successful bronchoplasty, *i.e.*, complete reinflation of the lung with permanent establishment of an adequate bronchial lumen, as judged by bronchoscopy, roentgenograms and bronchograms, was accomplished in nine of the 15 animals (Fig. 1). When bronchoplasty was infeasible or unsuccessful, the most common reason for failure was a stenotic segment too long to allow ideal anastomosis. Even after successful bronchoplasty, the once chronically atelectatic lungs reinflated to only about ⅔ normal volume except when unusually high positive pressure was applied.

Repeat studies after reinflation of the atelectatic lungs demonstrated marked physiologic improvements as summarized in Table II. Three saturation-tension curves of one animal prior to atelectasis, during complete collapse of the left lung, and following reaeration of the lung are presented in Figure 2.

Discussion

A number of previous investigators have demonstrated that blood flow through the atelectatic lung is markedly reduced.[20-23] Moore showed that the ratio of the blood flow through the right lung to that in the left in the normal dog is 3:2, and, in studies on acute atelectasis with the chest closed in anesthetized animals, found an average of 17.5 per cent of the cardiac output passing through the atelectatic left lung.[21] Keeley, studying acutely and chronically atelectatic lung in dogs with the chest open, found an average of 15.6 per cent shunt.[22] In our study an average of 14 per cent of the cardiac output passed through the left lung atelectatic two and one-half to 32 weeks; the shunts were found to range from 0 to 28 per cent. The degree of shunting did not appear to be appreciably different in our "long-term" as compared to our "short-term" animals. Therefore, the results of this phase of our study compare closely with those of previous workers in spite of the elimination of the variables of anesthesia and open-chest preparations.

It occurred to us that our assumption, that the physiologic deficit we were measuring was the result of shunting through the atelectatic lung, required justification and

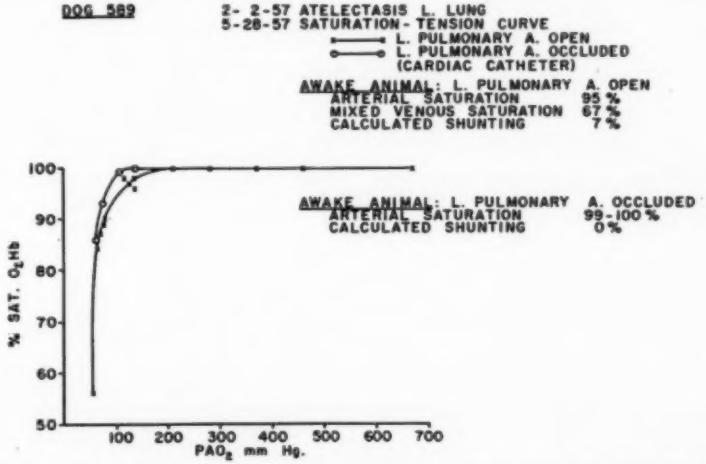

FIGURE 3, Dog 589: Saturation tension curve and above data obtained 15 weeks after production of complete collapse of the lung revealed seven per cent right-to-left anatomic shunting. Occlusion of the left pulmonary artery by balloon-tipped cardiac catheter resulted in disappearance of the right-to-left shunt.

control. These were obtained by an experiment in which the pulmonary artery to an atelectatic lung of 15-weeks' duration was intubated with a triple lumen balloon-tipped cardiac catheter. Inflating the balloon occluded the left pulmonary artery, while deflating it allowed blood flow to resume. A normal saturation-tension curve was obtained during occlusion of the pulmonary artery to the atelectatic lung, while a 7 per cent shunt was demonstrated with both pulmonary arteries patent (Figure 3).

There is no doubt that chronic atelectasis is at least partially reversible. Grossly, no difference was noted in the ease with which the "long-term" and "short-term" atelectatic lungs reinflated at surgery. Physiologically, following successful bronchoplasty, the average shunting was approximately 1 per cent of the cardiac output, signifying a marked improvement as compared to the studies prior to reinflation.

In view of this physiologic improvement resulting from reaeration, further studies were undertaken to assess the degree to which the reinflated, once atelectatic, lung resumes normality. Three animals that had undergone successful bronchoplasty with apparently complete reaeration of the left lung for six, seven and ten weeks were subjected to right pneumonectomy. This provided a preparation in which the re-expanded lung alone remained to support the animal's life; these dogs survived for 24 to 48 hours. Clinically, the postoperative course was one of excellent, immediate recovery with rapid, progressive deterioration characterized by vomiting, dyspnea and finally death. Post-mortem examination revealed boggy edematous lungs, congested livers and dilated right ventricles. Microscopic sections revealed striking hyperemia of the lungs, and acute passive congestion of the liver.

To more clearly define this abnormality, a balloon-tipped cardiac catheter was passed into the right pulmonary artery of an animal in which the left lung had been re-expanded for three weeks. While no shunt was demonstrable with the right pulmonary artery open, occluding it resulted in immediate fall in saturation from 98 per cent to 88 per cent. The reason for this is not entirely clear, the right bronchial tree remained fully ventilated during the entire experiment, and so may have constituted physiologically significant added dead space when the right pulmonary artery was occluded. Of more significance is the fact that acute pulmonary hypertension was produced when the entire cardiac output was diverted through the reinflated left lung by occluding the right pulmonary artery. Pre-occlusion right pulmonary artery pressure was 23/2 mm. Hg., while post-occlusion pressure proximal to the balloon was 83/18 mm. Hg. Roentgenograms made before and after occlusion demonstrate right ventricular dilatation following inflation of the balloon. Thus, we suspect that the reaerated lung contains abnormalities in the form of increased pulmonary vascular resistance which only become manifest in the absence of the contralateral normal lung. We wish to emphasize, however, that our report on this phase of the problem is preliminary and does not warrant firm conclusions. Further studies along these lines are in progress.

SUMMARY

Atelectasis of the entire left lung was produced in 15 dogs by chemical cautery of the left mainstem bronchus. After two and one-half to 32 weeks of atelectasis, physiologic deficit was measured in the awake, unsedated animal with the aid of a continuous recording oximeter. An average of 14 per cent of the cardiac output was found to be flowing through the atelectatic lung. The stenotic segment of the bronchus was later resected, the lung reaerated, and the animal was subsequently again evaluated physiologically. Postoperatively, an average of 1 per cent shunting was found, representing significant improvement in pulmonary function with reinflation of the atelectatic lung. Evidence of increased pulmonary vascular resistance in the reaerated lung is presented.

On the basis of these studies it is concluded that the chronically atelectatic lung should be reaerated in preference to resection, and that such reinflation will almost invariably result in improvement of the physiologic status.

RESUMEN

Se produjo la atelectasia del pulmón izquierdo en 15 perros por medio de la cauterización química del bronquio principal. Después de dos y media a treinta y dos semanas de atelectasia, se midió el déficit fisiológico en el animal despierto, no sedado, con la ayuda del oxímetro de registro contínuo.

Se encontró que a través del pulmón atelectásico estaba pasando el 14 por ciento del rendimiento cardiaco. El segmento estenosado del bronquio, fué después resecado, re-aereado el pulmón y después el animal fué estudiado de nuevo fisiológicamente.

Se encontró después de la operación que había un término medio de intercomunicaciones de 1 por ciento representando una mejoría significativa en la función pulmonar con la reinsuflación del pulmón atelectásico.

Se presentó evidencia de aumento de la resistencia vascular en el pulmón reaereado.

Según estos estudios, se concluye que el pulmón crónicamente atelectásico, debe ser reaereado en lugar de resecado y que tal reinflación dará por resultado invariablemente una mejoría fisiológica.

RESUME

L'atélectasie du poumon gauche dans sa totalité fut produite chez 15 chiens par cautère chimique de la bronche souche gauche. Après un temps allant de deux semaines et demies à 32 semaines d'atélectasie, le déficit physiologique fut mesuré chez l'animal éveillé, sans sédatif, grâce à un oxymètre à enregistrement continu. Une moyenne de 14% du débit cardiaque fut trouvée circuler à travers le poumon atélectasique. Le segment sténosé de la bronche fut ensuite réséqué, le poumon aéré de nouveau, l'animal fut de nouveau testé physiologiquement. Après l'intervention, une moyenne d'un pour cent de shunt fut trouvée, représentant une amélioration nette de la fonction pulmonaire, avec reventilation du poumon atélectasique. Les auteurs donnent la preuve de l'augmentation de la résistance des vaisseaux pulmonaires dans le poumon reventilé. En se basant sur ces études, ils concluent que le poumon chroniquement atélectasique devrait être reventilé de préférence à la résection, et qu'une telle reventilation apportera presque invariablement une amélioration de la condition physiologique.

ZUSAMMENFASSUNGEN

Atelektase der ganzen linken Lunge liess sich an 15 Hunden erzeugen durch chemische Aetzung des linken Hauptbronchus. Nach 2½ bis 32 Wochen dauernder Atelektase wurde das physiologische Defizit ermittelt am wachen, nicht beruhigten Tier mit Hilfe eines fortlaufend schreibenden Oximeters. Es fand sich, dass durchschnittlich 14% des Herzminuten-Volumens die atelektatische Lunge durchströmt. Dass stenotische Segment des Bronchus wurde später reseziert, die Lunge wieder beatmet, und das Tier wurde anschliessend wieder in physiologischer Form ausgewertet. Postoperativ fand sich durchschnittlich 1% Shunt; das bedeutet eine beträchtliche Besserung in der Lungenfunktion mit Wiederaufblähung der atelektatische Lunge. Es wird Beweis geführt für einen erhöhten pulmonalen Gefässwiderstand in der wiederbeatmeten Lunge.

Auf der Grundlage dieser Untersuchungen wird geschlossen, dass man es vorziehen sollte, die chronisch-atelektatische Lunge wieder zu beatmen anstatt sie zu resezieren. Eine solche Wiederaufblähung führt so gut wie immer zu einer Besserung des physiologischen Status.

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Sputum Viscosity and Postoperative Pulmonary Atelectasis*

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The relationship between changes in the viscosity of sputum and the development of pulmonary atelectasis has been discussed.[1-5] The fibers found in sputum which appear to be responsible for the viscosity are

TABLE I
VISCOSITY OF SPUTUM BEFORE AND AFTER OPERATION UNDER GENERAL ANESTHESIA

Case Number	1	2	3	4	5	6	7
Number of Days							
—7	105						
—6	305 206						
—5	73 173						
—4	221 67					323	
—3	305 160					346 309	
—2	320 80		24	19	111	342 570	54 34
—1	235 160	58 370	193 33	132 20	119 84	453 789	18 37
Day of Operation under General Anesthesia							
+1	948 423	1,087 1,080	727 571	1,007 204	327 317	1,440 973	187 151
+2	250 184	757 341	715 476	266 179		752 606	51 12
+3	82 94	346 535	465 450	71 85		291 514	109 44
+4		503 460	259 81	75 28		382	55 51
+5		590	8 98	59 67			109 45
+6			8 67	61 85			62 57
+7			7	45			28

The figures are the degrees of deflection on the viscometer produced by sputum expectorated through the day and overnight—more viscous sputum producing greater deflection, according to the method.[6]

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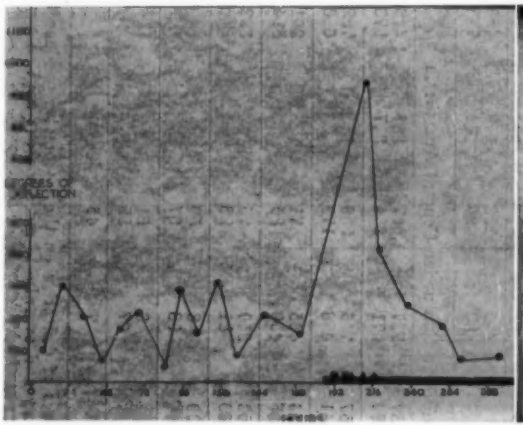
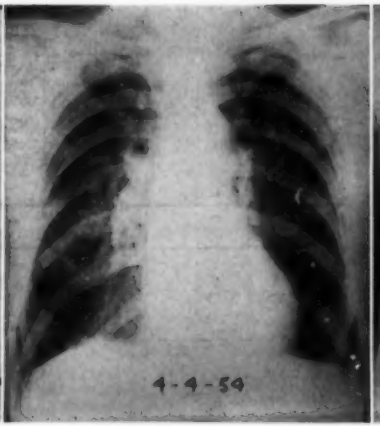
This work forms part of a University of Cambridge M.D. thesis.





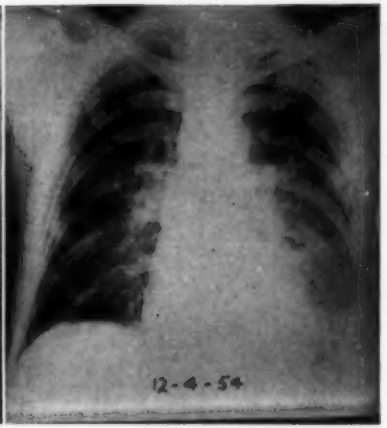


FIGURE 1A FIGURE 1B FIGURE 1C

Figure 1A: Sputum viscosity measurements before and after operation showing the increase at the time of operation and the development of postoperative pulmonary atelectasis is illustrated in Figures 1B and 1C. *Figure 1B:* Preoperative chest x-ray on Case 1. *Figure 1C:* Postoperative chest x-ray on Case, showing atelectasis of the left lower lobe.

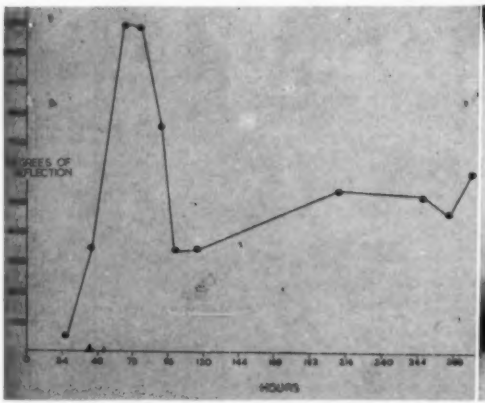


FIGURE 2A FIGURE 2B FIGURE 2C

Figure 2A: Sputum viscosity measurements before and after operation, showing the increase at the time of operation. The development of postoperative pulmonary atelectasis is illustrated in Figures 2B and 2C. *Figure 2B:* Preoperative chest x-ray on Case 2. *Figure 2C:* Postoperative chest x-ray on Case 2 showing atelectasis in the right lower lobe.

TABLE II
RELATING THE SIZE AND DURATION OF THE INCREASE IN VISCOSITY OF SPUTUM TO PREMEDICAMENTS AND ANESTHETIC AGENTS AT OPERATION

Case Number:	1	2	3	4	5	6	7
Basal viscosity increased by:	5x	2x	7x	6x	3x	3x	....
Duration of viscosity rise in hours:	36	60	89	66	....	24	....
Premedication							
Omnopon (mgm.)	22	22	....	....	11	11	....
Scopolamine (mgm.)	0.4	0.4	0.6	0.4	0.2	....	0.4
Pethidine (mgm.)	250	....	250	200	....	....	100
Morphine (mgm.)	32	....	....	16	....	....	....
Atropine (mgm.)	....	....	....	....	....	0.6	....
Anesthetic							
Oxygen	+	....	+	+	....	....	+
Nitrous oxide	+	....	+	+	....	....	+
Ether	....	....	....	+	....	....	....
Cyclopropane	....	+	....	....	+	....	+
Thiopentone	+	+	+	+	+	+	+
Tubarine	+	....	+	....	....	+	+
Trichlorethylene	....	....	....	+	....	....	....
Pethidine	+	....	....	+	....	....	+
Succinyl choline	....	....	....	+	....	+	....

mucoprotein and deoxyribonucleoprotein; the former is formed in the goblet cells of the bronchial mucosa and the mucous secreting submucosal glands, whilst the latter is formed from the nuclear deoxyribonucleic acid of degenerating pus cells. This work was an attempt to measure changes in viscosity during the operative period and to investigate some of the influencing factors.

Method

The patients studied were in hospital for elective surgery. They were suffering from chronic bronchitis which was in a stable phase—neither developing nor recovering from an acute infection, nor were they having

TABLE III
THE EFFECT OF ATROPINE ON THE VISCOSITY OF SPUTUM
(Degrees of Deflection on the Viscometer)

Before atropine	31	372	204	236	92	286
	19	452	285	283	45	587
	1 mgm. s.c.		0.5 mgm.			
After atropine	15	55	138	119	167	468
		72	325	193		427

TABLE IV

THE EFFECT OF PETHIDINE ON THE VISCOSITY OF SPUTUM

(Degrees of Deflection on the Viscometer)

Daily measurements of viscosity before pethidine				52
				162
				20
				125
	174			38
	270			249
	227	254		35
	442	295	52	180
	490	303	32	219
	269	281	20	275
	254	342	30	212
After pethidine	Pethidine 100 mgm. intramuscularly			50 mgm. intramuscularly
	622	525	66	455
	297	481	124	37
	369	290	58	

changing medicinal therapy. They were expectorating a constant amount of mucoid sputum and measurements of the viscosity were made using the technique described elsewhere.[6]

The effect of operating under general anesthesia was investigated in seven instances; one patient had two operations. The effect of atropine was investigated on six occasions, subcutaneous injection of 1 mgm. in two and 0.5 mgm. in four instances. Pethidine, 100 mgm. intramuscularly in three patients and 50 mgm. in another patient was investigated. Codeine phosphate, 22 mgm. intramuscularly in three and 65 mgm. orally in another patient was tried.

Results

Measurements of the viscosity of the sputum expectorated by these patients before and after operation are shown in Table I; details of premedication and anesthetic agents used are shown in Table II. Figures 1A and 2A show the increase in viscosity in two patients who had the misfortune to develop postoperative pulmonary atelectasis illustrated in Figures 1B and 1C in the first patient, and in Figures 2B and 2C in the second. The effects of atropine, pethidine and codeine are shown in Tables III, IV and V respectively.

TABLE V

THE EFFECT OF CODEINE ON THE VISCOSITY OF SPUTUM

(Degrees of Deflection on the Viscometer)

Daily measurements of viscosity before codeine	31		190	
	149	166	203	81
	49	460	543	52
	120	549	600	42
After codeine	22 mgm. i.m.			65 mgm. orally
	180	766	1,065	255
	51	120	593	164
	112	440	175	126

Discussion

The efficient expectoration of sputum depends on ciliary activity, air flow during quiet respiration or coughing and bronchial movement; ciliary activity is impaired by deviations of viscosity from the normal ideal range.[7] The viscous nature of sputum is mainly due to the fibers of mucoprotein and deoxyribonucleoprotein which it contains. Increasing the viscosity impairs sputum expulsion and the consequent sputum retention predisposes to the development of bronchial occlusion and atelectasis. The various factors affecting the viscosity at the time of operation have been discussed in detail[2]; the more important are the state of body hydration, drugs—used for premedication, anesthesia or postoperative pain—and the depth and duration of anesthesia. The development of postoperative pulmonary atelectasis in Cases 1 and 2 coincided with the maximum increase in sputum viscosity; the preoperative measurements in Case 1 illustrate the diurnal variation, overnight sputum being more viscous than that produced during the day. Correlating the extent and duration of the increase in viscosity with drugs used for premedication, Cases 1, 3 and 4 received more morphine and pethidine than the other cases (Table II).

Examination of the results from the experiments with atropine reveals no significant increase in viscosity; atropine abolishes the neurogenically controlled submucosal gland secretion, effecting a quantitative rather than a qualitative change in the bronchial secretion. Goblet cell secretion, and the vehicle formed by transudation from the pulmonary vascular bed, are presumably not influenced by atropine. The increased viscosity following pethidine administration suggests that this drug should be used with caution in patients with chronic respiratory disease. After the administration of codeine phosphate, the apparent increase in viscosity substantiates the observations of Basch[9] and Folken.[10] Hillis,[11] investigating the effect of drugs on the cough reflex, found codeine without effect in contradistinction to morphine, diamorphine and amidone which were powerful suppressives and will consequently produce sputum retention.

SUMMARY

Change in the viscosity of sputum expectorated by patients suffering from chronic bronchitis in a stable phase, was measured. Operation under general anesthesia produced an increase in viscosity which, in two patients, was associated with the development of postoperative pulmonary atelectasis. Atropine produced no apparent increase in viscosity while there was some increase after pethidine and codeine.

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RESUMEN

Se ha medido el cambio en la viscosidad del esputo expectorado por enfermos de bronquitis crónica en fase estable.

La operación bajo anestesia general produjo un aumento de la viscosidad que en dos enfermos fué asociado con la presencia de atelectasia pulmonar postoperatoria.

La tropina no produjo aparente aumento de la viscosidad en tanto que sí lo hubo después de pethidina y de la codeina.

RESUME

Les modifications de la viscosité de l'expectoration des malades atteints de bronchite chronique furent mesurées alors que ces malades étaient en période stable. Une intervention sous anesthésie générale produisit une augmentation de la viscosité qui, chez deux malades, entraina une atélectasie pulmonaire post-opératoire. L'atropine ne produisit aucune augmentation apparente de la viscosité tandis qu'il y eut une augmentation après l'administration de péthidine et de codéine.

ZUSAMMENFASSUNGEN

Es wurden die Veränderungen in der Viskosität von Sputum gemessen bei Kranken mit chronischer Bronchitis in einer stabilen Phase. Operationen unter Vollnarkose führten zu einem Anstieg in der Viskosität; diese war bei 2 Patienten vehknüpft mit dem Auftreten postoperativer pulmonaler Atelektasen. Atropin bewirkte keine augenfällige Zunahme der Viskosität; jedoch ergab sich eine gewisse Zunahme nach Pethidin oder Codein.

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Diagnosis of Bronchogenic Carcinoma: An Evaluation of Pulmonary Cytology, Bronchoscopy and Scalene Lymph Node Biopsy

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Roentgenographic examination of the chest usually serves as a screening procedure for the detection of suspicious pulmonary lesions, but in most instances it does not permit a definitive diagnosis of bronchogenic carcinoma. Visualization and biopsy of the neoplasm via the bronchoscope provides the most conclusive evidence but discloses only about one third of lung cancers. The combination of a suspicious pulmonary lesion by x-ray examination and a positive lymph node biopsy, usually anterior scalene lymph node biopsy, is found in 20 to 50 per cent of bronchogenic cancers, thus providing strong presumptive evidence of primary lung tumor.[1-6] The cytologic examination of sputum, bronchial secretions, or pleural fluid should be positive in 75 per cent of patients who have lung cancer. The diagnostic triad of bronchoscopy, scalene lymph node biopsy, and cytologic examination of sputum or bronchial secretions should detect nine of 10 primary lung carcinomas.[4]

In routine practice it is not always possible, or desirable, to utilize all these diagnostic procedures. The purpose of this report is to present the results of a consecutive series of routine diagnostic examinations of patients who had proved bronchogenic cancers, to determine the practical value of each of these three techniques and to compare their relative merits.

Materials and Methods

The records of 100 consecutive patients who had histologically confirmed lung cancer were analyzed. Only patients who were admitted in a terminal condition which precluded diagnostic studies were excluded. The correlation between roentgenographic findings and the results of other diagnostic procedures will be reported elsewhere.

Eighty-four patients had bronchoscopic examinations. Contraindications or technical difficulties precluded this examination in the other 16 patients. Routine bronchoscopic examination included the aspiration of bronchial secretions or bronchial washings for cytologic examination.

Seventy-eight anterior scalene lymph node biopsies were attempted. The number of lymph nodes obtained in each biopsy specimen varied from 0 to 19, with a mean of 4.5 per specimen. The right scalene fat pad was removed when the lesion was in the right lung or in the lower lobe of the left lung, unless lymph nodes were palpable on the left side. Left scalene lymph node biopsy was reserved for lesions in the left upper lobe. Pathologic examinations of the tissue consisted of the microscopic study of all grossly visible lymph nodes; if these lymph nodes did not contain neoplasm, all of the remaining tissue was embedded and sectioned.

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Four hundred and forty sputum specimens were examined cytologically, but 70 (15 per cent) were not "deep-cough" specimens and were rejected as unsatisfactory. Although the cytologic examination consisted of the study of at least three adequate specimens when possible, less than one half of the patients had the benefit of such a complete examination and, in six cases no sputum was examined. Rarely, incomplete studies were due to the inability of the patient to raise sputum.

Neoplasms of upper lobes outnumbered those in lower lobes two to one; there were nine tumors which either extended into both upper and lower lobes or were confined to main-stem bronchi; the latter have been classified separately (Fig. 4).

Results and Discussion

The *combined cytologic studies* of sputum, bronchial secretions, and pleural fluid gave more positive results (76 per cent) than did bronchoscopy and lymph node biopsy combined (60 per cent) (Fig. 1). However, since the cytologic study of bronchial secretions is part of bronchoscopic examination, it seems more logical to combine it with the results obtained by

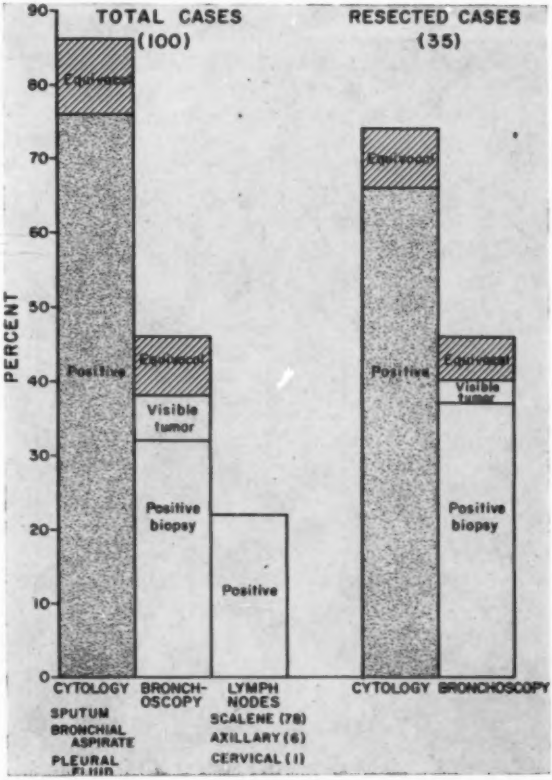

FIGURE 1: Results in 100 proved bronchogenic carcinomas, 35 of which were resected. *Note:* The "visible tumors" are those which had negative bronchial biopsies but were seen on bronchoscopy.

visualization of the neoplasm and by bronchial biopsy. These modified figures indicate that the sensitivity of bronchoscopy is almost equal to the cytologic examination of sputum, particularly in the resected cancers (Fig. 2).

More than 40 per cent of the patients who had thoracotomy had positive cytologic smears as the only preoperative microscopic support of the clinical diagnosis. Similar findings were reported by Woolner and McDonald,[7] and by Gibbon and associates.[8]

Cytologic examination of sputum: Sixty-three of the 100 patients had positive smears of sputum, and another nine had smears which were interpreted as suspicious for malignant cells (Fig. 2).

Twenty-seven of the *initial* sputa were positive for malignant cells; 17, suspicious; eight, unsatisfactory; and six patients had no cytologic examination. Thus, although less than one third of the first examinations were definitely positive, over 50 per cent of the adequate specimens (44 of 86) were positive or suspicious, indicating the need for additional diagnostic studies. The value of multiple examinations is illustrated in Figure 3. The percentage of positive results increased from 30 per cent in the case of a single examination to 96 per cent when more than five specimens were studied.

Although the highest accuracy for sputum examination was obtained in the diagnosis of carcinomas in main-stem bronchi or in lower lobes, more than one half of those in upper lobes exfoliated detectable malignant cells.

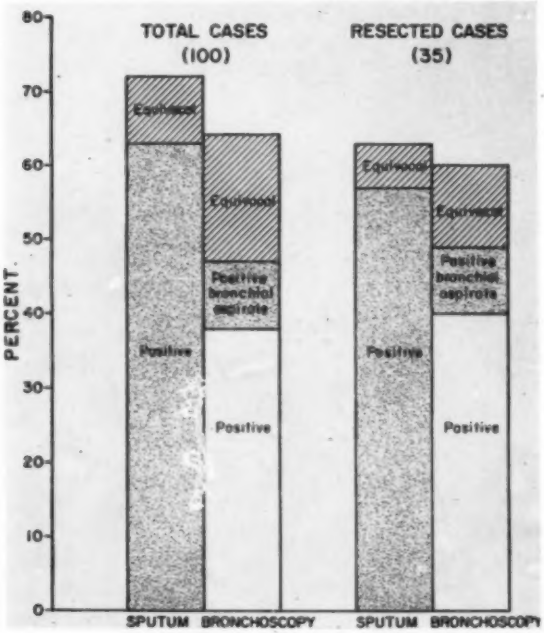

FIGURE 2: Sputum versus bronchoscopy. The latter includes the cytologic examination of bronchial washings.

This is especially significant since only 13 of the 60 tumors of upper lobes were visualized on bronchoscopy (Fig. 4). Similarly, when the neoplasms were considered in respect to their locations within lobes, better cytologic results were found in the case of hilar tumors; but most of these were readily detected by bronchoscopy while bronchoscopic biopsy was invariably negative when the cancers were peripheral in location (Fig. 5).

Although the histologic type of the tumor had no striking effect on cytologic results, epidermoid carcinomas gave the best results because they are usually in large bronchi, and the cells are recognized most readily (Fig. 6). Undifferentiated-cell carcinomas also frequently are located in the larger ramifications of the bronchial tree, but the small undifferentiated cells ("oat-cells") are overlooked more easily in the smears. It is not surprising that cytologic success with the adenocarcinomas was less impressive, since they often are located peripherally.

During the period covered by this report, more than 1,000 sputum specimens from 412 patients were studied. *There were two false positive reports, an incidence of 0.2 per cent.*

Bronchoscopic examination yielded 32 positive bronchial biopsies, six

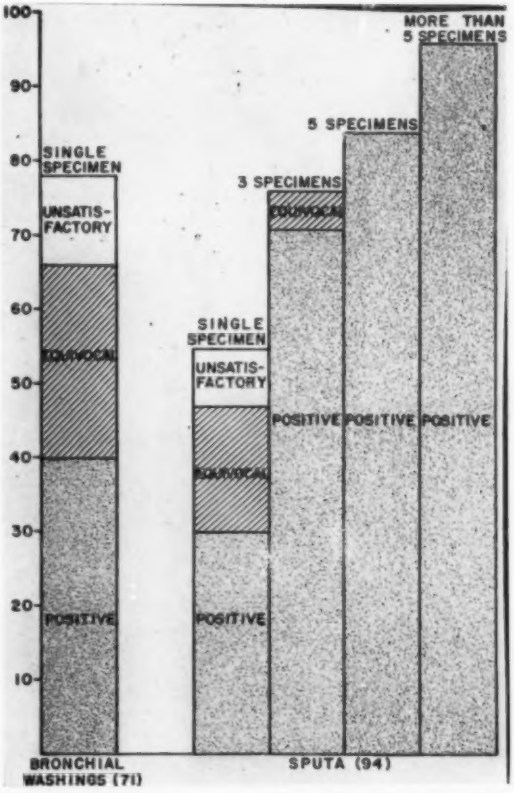

FIGURE 3: Bronchial washings versus sputum. Significance of multiple examinations.

visible tumors which could not be biopsied and nine negative visual findings but positive bronchial washings (Fig. 2). Seventeen other patients had equivocal findings such as: suspicious cytologic smears, bronchial stenosis, deformity, or extrinsic bronchial compression. The poor results of bronchoscopy in the diagnosis of carcinomas of upper lobes, or of peripheral carcinomas are illustrated in Figures 4 and 5. Since tumors of upper lobes are twice as numerous as those in lower lobes, the overall accuracy of bronchoscopy decreases appreciably. The addition of cytologic examination of bronchial washings increased the accuracy of bronchoscopic diagnosis of upper lobe lesions from 22 to 38 per cent and permitted the diagnosis of five of the peripheral tumors, none of which was visible through the bronchoscope. The results of bronchoscopy combined with the cytologic examination of bronchial secretions compared favorably with the cytologic examination of a *single* specimen of sputum, but the situation was reversed when more than one sputum sample was examined (Fig. 3). The low percentage of positive results and the high incidence of unsatisfactory specimens or equivocal findings with bronchial washings are attributed to the fact that the bronchoscopic examinations were per-

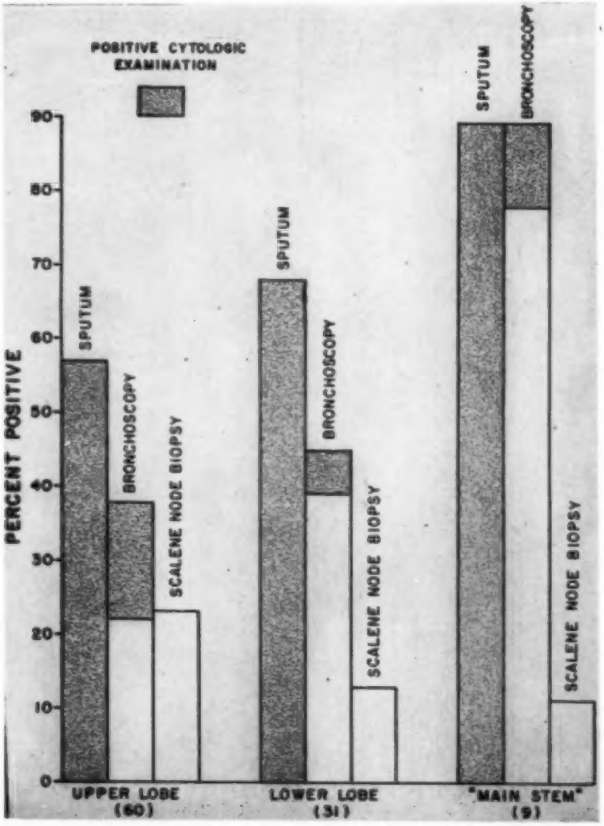

FIGURE 4: Comparative results in diagnosis of cancers of upper versus lower lobes.

formed by trainee-physicians who had relatively little experience in the technique of obtaining satisfactory bronchial specimens.

Fourteen patients had positive bronchoscopic findings (including cytologic examination of bronchial secretions) but negative sputa or scalene lymph node biopsy.

Scalene lymph node biopsy was the least sensitive diagnostic modality (Figs. 1 and 3 to 6). In only two instances did it provide the only microscopic evidence of malignancy prior to operation or necropsy. However, when positive, it provides not only diagnostic confirmation but also a criterion of inoperability.

The likelihood of finding cancer in scalene lymph nodes is almost doubled when the carcinoma is in an upper lobe (Fig. 4). Previous reports have stressed the poor results with tumors of lower lobes.[4, 6] However, Horwitz and Findlay[5] found positive lymph nodes in six of nine carcinomas of lower lobes.

Squamous cell carcinomas are least likely to provide positive scalene lymph node biopsies (Fig. 6), an observation which has been made repeatedly.[3-6] Only four of the epidermoid cancers in this series had metastasized to scalene lymph nodes at the time of the biopsy.

The importance of removing sufficient tissue has been emphasized by Connar[6] who regarded any specimen containing less than four lymph nodes as unsatisfactory. Using Connar's criterion, 28 of the scalene lymph node biopsies in this series would be unsatisfactory. Horwitz and Findlay[5] obtained positive nodes from 24 of 44 patients and attributed their success to a clearing technique for the isolation of lymph nodes from the fat pad. We have attempted this method, but abandoned it because it delayed the preparation of microscopic sections without increasing the positive results. Since we embed and section the entire scalene fat pad before a negative report is submitted, it may be that the lower percentage of successful biopsies in our series is a reflection of the amount of tissue removed at operation.

CONCLUSIONS

1. A positive cytologic examination was the only microscopic evidence of carcinoma in over 40 per cent of the *resected* neoplasms of the bronchus and more cancers were detected by this method than by bronchoscopy and scalene lymph node biopsy combined, unless bronchoscopy included the cytologic examination of bronchial secretions.
2. Positive or suspicious smears were obtained from 44 of 94 bronchogenic carcinomas by a single cytologic examination of sputum. The percentage of positive smears increased to 71 per cent when three specimens were examined and to 96 per cent when more than five were studied.
3. Cytologic examination of sputum was of greatest practical value in the diagnosis of cancers in upper lobes or in the periphery of lungs where bronchoscopy usually fails.
4. The cytologic examination of bronchial washings almost doubled the number of cancers of upper lobes detected by bronchoscopy.
5. Peripheral carcinomas were much more frequently detected by sputum examination than by bronchial washings.
6. Anterior scalene lymph node biopsy was positive in only 22 of 78 patients and was of most value in the diagnosis of undifferentiated-cell carcinomas or adenocarcinomas of upper lobes. Only four squamous cell carcinomas yielded positive biopsy regardless of location and despite the fact that this was the most common tumor.

RESUMEN

1. La citología positiva fué la única evidencia microscópica de más de 40 por ciento de neoplasias bronquiales resecadas y se descubrieron más cánceres por este método que por la broncoscopía y la biopsia de escalenos juntas, a menos que la broncoscopía incluyese el examen de las secreciones bronquiales.

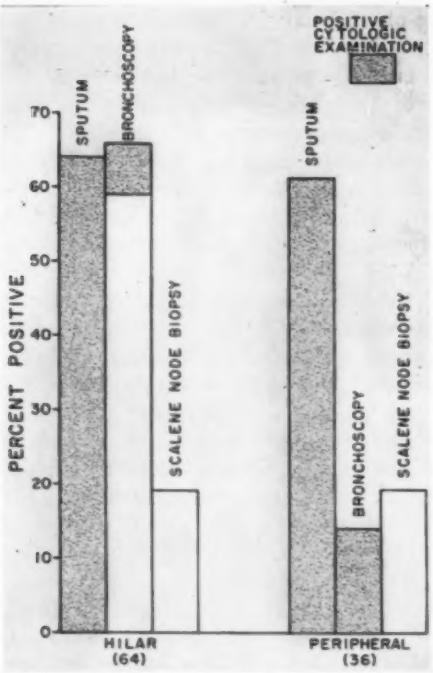

FIGURE 5: Comparative results in diagnosis of peripheral versus hilar cancers.

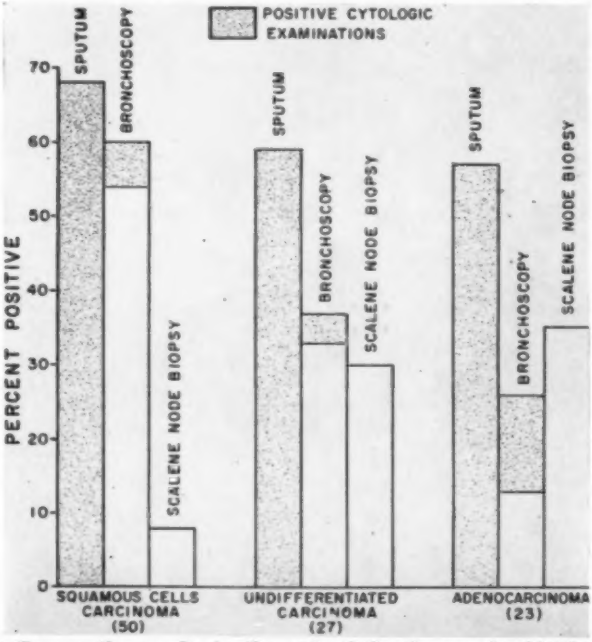

FIGURE 6: Comparative results in diagnosis of the three major histologic types of bronchogenic cancer.

2. Se obtuvieron frotis positivos o sospechosos de 44 de 94 carcinomas bronquigénicos por un solo examen citológico. El porcentaje de frotis positivos ascendió a 71 cuando se usaron tres especímenes y a 96 por ciento cuando más de cinco se observaron.
3. El examen citológico del esputo fué del mayor valor práctico en el diagnóstico de cánceres del lóbulo superior o de la periferia del pulmón cuando la broncoscopía generalmente fracasa.
4. El examen citológico de lavados bronquiales casi dobló el número de cánceres de lóbulo superior descubiertos por broncoscopía.
5. Los carcinomas periféricos son mucho más frecuentemente descubiertos por el examen de los esputos que por el lavado bronquial.
6. La biopsia de ganglios pre-escalénicos fué positiva en 22 de 78 enfermos y fué de mayor valor en el diagnóstico de los carcinomas de céulas no diferenciadas o en los adenocarcinomas de los lóbulos superiores. Sólo cuatro carcinomas de células escamosas dieron biopsias positivas sin tener en cuenta la ubicación y a pesar de que ésta fué el tumor más frecuente.

RESUME

1. Un examen cytologique positif fut la seule preuve microscopique de cancer dans plus de 40% des exérèses pour cancer bronchique. On découvrit plus de cancers par cette méthode que par l'ensemble des biopsies soit par bronchoscopie soit par examen des ganglions de la région préscalénique, sauf quand la bronchoscopie comportait l'examen cytologique des sécrétions bronchiques.
2. Des frottis positifs ou douteux furent obtenus pour 44 des 94 cancers bronchiques par un seul examen cytologique de l'expectoration. Le pourcentage de frottis positif s'éleva à 71% quand trois lames furent examinées, et à 96% quand il y en eut plus de cinq étudiées.
3. L'examen cytologique de l'expectoration fut d'une très grande valeur pratique dans le diagnostic des cancers des lobes supérieurs ou des régions périphériques des poumons, circonstances dans lesquelles la bronchoscopie est habituellement en échec.
4. L'examen cytologique des lavages bronchiques donne presque deux fois plus de cancers des lobes supérieurs que la bronchoscopie.
5. Les cancers périphériques furent beaucoup plus fréquemment mis en évidence par l'examen de l'expectoration que par les lavages bronchiques.
6. La biopsie du ganglion pré-scalénique ne fut positive que dans 22 cas sur 78 malades, et fut de plus grande valeur dans le diagnostic de cancers à cellules indifférenciées ou dans les adénocarcinomes des lobes supérieurs. Quatre cancers seulement à cellules épidermoïdes donnèrent lieu à des biopsies positives, sans rapport avec le si ège et malgré le fait que c'était la tumeur la plus fréquente.

ZUSAMMENFASSUNGEN

1. Eine positive cytologische Untersuchung war der einzige mikroskopische Beweis des Carzinoms in über 40% der *resezierten* bronchialen Neoplasmen; und es wurden mehr Restfälle durch diese Methode entdeckt als durch die Bronchoskopie in Kombination mit Skalenus-Lymphknoten-Biopsie, sofern nicht die Bronchoskopie die cytologische Untersuchung des Bronchialsekretes einschloss.
2. Positive oder verdächtige Ausstriche wurden gewonnen bei 44 von 94 Bronchuscarzinomen durch eine einzige cytologische Sputumuntersuchung. Der Prozentsatz von positiven Ausstrichen stieg bis auf 71% an, falls 3 Präparate untersucht und bis auf 96%, wenn mehr als 5 geprüft wurden.
3. Cytologische Untersuchung des Sputums erwies sich als von grösstem praktischen Wert zur Diagnose von Oberlappenkrebsfällen oder solchen in den peripheren Lungenabschnitten, bei denen die Bronchoskopie gewöhnlich versagt.
4. Die cytologische Untersuchung von Bronchialspülflüssigkeit verdoppelte meistens die Zahl der durch die Bronchoskopie entdeckten Oberlappenkrebsfälle.
5. Periphere Carcinoms wurden viel häufiger durch Sputumuntersuchungen gefunden als durch solche des Bronchial-Spülwassers.
6. Lymphknotenbiopsie am vorderen m. Scal. waren nur in 22 von 78 Kranken positiv und war von besonderem Wert bei der Diagnose von Carzinomen mit undifferenzierten Fällen oder Adenocarzinomen der Oberlappen. Nur 4 Klassenzellcarzinome hatten positive Biopsien unbeschadet der Lokalisation und trotz der Tatsache, dass dies der häufigste Tumor war.

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SECTION ON CARDIOVASCULAR DISEASES

Observations on Isobutamide in Patients with Heart Failure*

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The clinical effectiveness of carbonic anhydrase inhibitors is well established but their usefulness appears to be limited because of tolerance and potency factors. Consequently, it is necessary to continue investigation on new compounds of this type. This report describes the clinical use of the isobutyl derivative of Diamox (acetazoleamide) (Fig. 1) and compares its effectiveness with that of acetazoleamide (Diamox) in patients with mild to moderately severe congestive heart failure.

Methods and Materials

The observations in this report were made on two groups of patients. One group of 20 ambulatory cardiac patients were given both Acetazoleamide (Diamox) and Isobutamide and the results compared for clinical effectiveness. A diuretic biossay study was done on a second group of eight patients in the metabolic ward of the hospital.

Observations on Clinical Response

An evaluation of the clinical effectiveness and comparative response to the two drugs was conducted in the diuretic clinic. The 20 ambulatory cardiac patients were in a state of mild to moderately severe congestive heart failure, and all had been on a daily maintenance dose of digitalis and had been receiving parenteral mercurial therapy one or two times a week. The sodium intake in this group of patients was variable since their meals were not made under conditions of strict dietary control.

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ACETAZOLEAMIDE

(Diamox)

ISOBUTAMIDE

Structural Formulas of Isobutamide and Diamox.

FIGURE 1: Comparison structural formula of acetazoleamide (Diamox) and isobutamide.

The sex in this group of patients was equally distributed and the age ranged from 35 to 80 years. The etiology of the heart failure was arteriosclerotic heart disease in 15 and chronic rheumatic valvular heart disease in five. Placebos were substituted for the diuretics for two weeks before the start of this study but the digitalis was continued without alteration throughout the study.

The patients were divided into two sub-groups (A and B) of 10 each. Control weights were established in each patient after two weeks without diuretics and then Group A was given 250 mg. of Isobutamide* three times a day, and Group B was given 250 mg. of Diamox (acetazoleamide) three times a day for six weeks. At the end of this initial six week period diuretics were withheld for two weeks and then Diamox was given to Group A and Isobutamide to Group B for a period of six weeks employ-

*Furnished by Organon, Inc.

TABLE I—WEIGHT LOSS AFTER 6 WEEKS THERAPY WITH ISOBUTAMIDE AND ACETAZOLAMIDE (DIAMOX) (250 MG. THREE TIMES DAILY)

	Patient	Control Weight	Weight After Six Weeks of Isobutamide 250 mg. T.I.D.	Weight Change	Weight After 6 Weeks of Diamox 250 mg. T.I.D.	Weight Change
Group A	S. E.	170	168	—2	171	+1
	L. G.	119	114	—5	120	+1
	J. S.	165	163	—2	160	—5
	F. G.	158	157	—1	155	—3
	N. L.	115	110	—5	115	0
	K. G.	143	139	—4	141	—2
	N. N.	172	174	+2	173	+1
	W. S.	169	168	—1	168	—1
	M. W.	205	199	—6	202	—3
	C. B.	186	177	—9	179	—7
	Average	160	157	—3.3	158	—1.8

	Patient	Control Weight	Weight After 6 Weeks of Diamox 250 mg. T.I.D.	Weight Change	Weight After Six Weeks of Isobutamide 250 mg. T.I.D.	Weight Change
Group B	A. S.	114	108	—6	108	— 6
	F. A.	163	156	—7	157	— 6
	E. B.	102	100	—2	100	— 2
	H. C.	140	139	—1	138	— 2
	M. P.	137	134	—3	131	— 6
	A. P.	185	189	+4	183	— 2
	S. C.	106	110	+4	111	+ 5
	E. W.	252	247	—5	241	—11
	J. E.	127	123	—4	122	— 5
	J. R.	144	141	—3	142	— 2
	Average	147	145	—2.3	143	— 3.7

T.I.D.—Drug given 3 times a day.

ing the same dose as before. Finally, 150 mg. of Isobutamide was given twice a day to Group A for six weeks after these patients had not received diuretic therapy for a week. Twice a week, throughout the study, all patients were weighed and examined for severity of signs and symptoms of congestive heart failure and toxic effects.

Water and Electrolyte Excretion Studies

The effect of Isobutamide on water and electrolyte excretion was studied in eight patients under conditions of a controlled metabolic ward. Methods and techniques are those previously described (1). Eight cardiac patients were used for this study. They were free of edema and were on maintenance digitalis therapy. Their diet contained 50 mEq. of sodium daily. Control values for 24 hour urine and electrolyte excretion were established and then a daily dose of 250 mEq. of Isobutamide was administered orally for two days. The 24 hour urine and electrolyte excretions were determined. The patients were weighed daily before breakfast and after voiding. The average 24 hour increase in excretion of sodium, potassium, and water and weight loss for two days while receiving the drug were compared with control values.

The effect of prolonged daily administration of Isobutamide was observed in two patients by determining the daily sodium and water excretion for three weeks.

Results and Comments

Observations on Clinical Response

The results of this study (Group 1) are summarized in Table I and Figure 2.

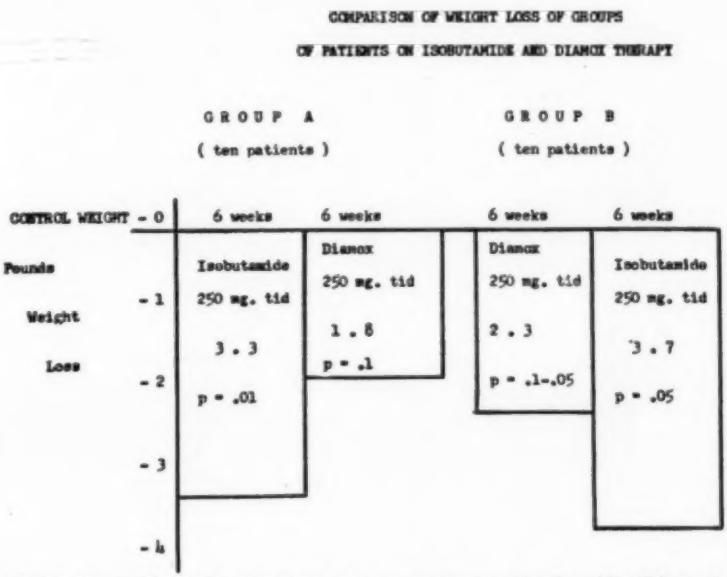

FIGURE 2: Comparison of weight loss as a response to acetazoleamide (Diamox) and isobutamide. The patients in Group A first received isobutamide for 6 weeks and then Diamox for 6 weeks. The patients in Group B first received Diamox and then isobutamide.

TABLE II—CLINICAL RESPONSE AND SIDE REACTIONS

	Side Reactions		Clinical Response with 6 weeks of Drug Therapy
	Anorexia	Nausea	
Isobutamide	2	2 (transient)	Symptoms of Congestive Failure Controlled No Mercurials
(Acetazoleamide) (Diamox)	2	0	Symptoms of Congestive Failure Controlled No Mercurials

The average weight loss at the end of the first six week period in Group A (Isobutamide) was 3.3 lbs. ($p < 01$) and Group B (Diamox) was 2.3 lbs. ($p < .05$). At the end of the second six week period after reversal of the drug being administered, the average weight loss for Group A was 1.8 lbs ($p = .1$) and Group B was 3.7 lbs. ($p < .05$). The average weight loss at the end of each six week period was quite comparable to the weight loss found after the second day of drug administration in each six week period. It has been reported that tolerance (1, 2, 3) to carbonic anhydrase inhibitors develops within several days. However, in the groups of patients described in our studies we found that a significant weight loss was maintained after prolonged administration of these agents and that the heart failure apeared to be well controlled without the use of mercurial diuretics. It apeared that the weight loss in both groups of patients (A and B) was greater while receiving Isobutamide than while receiving Diamox in similar dosage.

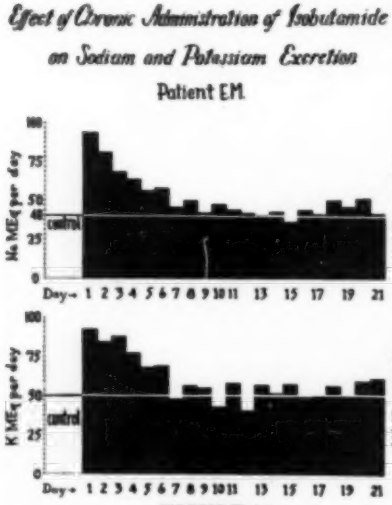
Effect of Chronic Administration of Isobutamide on Sodium and Potassium Excretion
Patient EM
Na MEq per day
K MEq per day
control
Day→ 1 2 3 4 5 6 7 8 9 10 11 13 15 17 19 21

FIGURE 3A

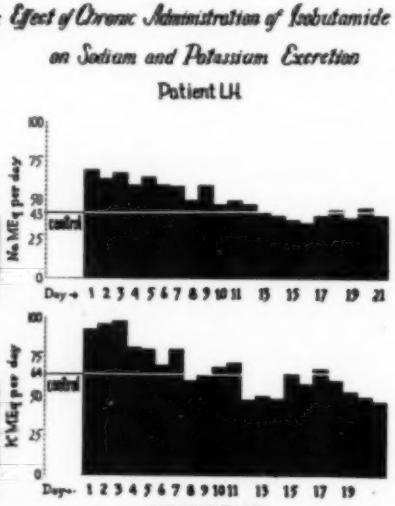
Effect of Chronic Administration of Isobutamide on Sodium and Potassium Excretion
Patient LH
Na MEq per day
K MEq per day
control
Day→ 1 2 3 4 5 6 7 8 9 10 11 13 15 17 19

FIGURE 3B

Figure 3A: Effect of continuous daily administration of 250 mg. of Isobutamide on sodium and potassium excretion. During the first day the increase in sodium excretion was more than 100% but this gradually decreased so that after one week the excretion rate was back to control values despite the continuous administration of the drug.—*Figure 3B:* The effect of continuous daily administration of Isobutamide on sodium and potassium excretion in another patient. The response was of a lesser magnitude but similar to the response summarized in Figure 3A.

TABLE III—SERUM ELECTROLYTE DETERMINATIONS IN THOSE PATIENTS SHOWING A DEPRESSION IN SERUM SODIUM BELOW 140 mEq. AFTER 6 WEEKS OF THERAPY

	Patient	NA	CO_2	Cl	Hg	Hct	W.B.C.
Isobutamide 250 mg. TID Six Weeks	C. B.	134	17	104	No	Change	
	K. G.	134	18	98	No	Change	
	N. Mc	133	14	97	No	Change	
	M. W.	139	19	98	No	Change	
	J. S.	137	18	100	No	Change	
	W. S.	137	19	94	No	Change	
	Patient	NA	CO_2	Cl	Hg	Hct	W.B.C.
Diamox Azetazoleamide 250 mg. TID Six Weeks	F. A.	139	17	102	No	Change	
	H. C.	135	16	100	No	Change	
	A. P.	134	15	99	No	Change	
	E. W.	138	17	102	No	Change	
	S. C.	137	19	77	No	Change	

TABLE IV—EFFECT OF ISOBUTAMIDE ON BODY WEIGHT, AND INCREASED EXCRETION OF WATER AND ELECTROLYTES [Average for First Two Days of Isobutamide (250 mg./day)] COMPARED WITH BUTAMIDE, DIAMOX AND CARDRASE

Patient	Increase in Sodium Excretion mEq/24 hr.	Increase in Potassium Excretion mEq/24 hr.	Changes in Chloride Excretion mEq/24 hr.	Increase in Water Excretion liters/24 hr.	Decrease in Weight (Kilograms)
Response to Isobutamide					
E. M.	46	38	— 9	0.25	—0.2
F. M.	8	18	—12	0.30	—0.2
L. N.	24	29	—13	0.20	—0.3
C. P.	78	25	—46	0.60	—0.4
J. K.	32	36	+ 4	0.00	—0.2
S. O.	18	43	—30	0.30	—0.5
J. P.	28	68	— 8	0.24	—0.4
S. C.	41	16	— 6	0.28	—0.1
Mean	34	34	—15	0.27	—0.28
P Value	< .01	.001	.05	.01	.001
Response to Butamide, Diamox, and Cardrase					
Butamide					
Mean (10 pts)	31	43	—11	.22	—0.2
P Value	< .001	.001	.10	.05	.05
Diamox (Acetazoleamide)					
Mean (10 pts)	35	36	— 9	.44	—.30
P Value	< .001	.001	.01	.001	.02
Cardrase (Ethoxzolamide)					
Mean (10 pts)	44	37	— 6	.43	—.57
P Value	< .001	.001	.10	.01	.01

The average weight loss for Group A at the end of six weeks while receiving 150 mg. of Isobutamide twice a day was 2.7 lbs. ($p < 0.01$). This was comparable to the weight loss after the second day while on this dose and compares favorably with the effects of the drug at the higher dosage schedule. This finding is probably a clinical demonstration of the absence of an increase in the diuretic effectiveness when the dose of carbonic anhydrase inhibitors has passed the "apex" point (1) which dose is somewhat below 250 mgm.

Side Reactions

There were two patients receiving Isobutamide that complained of nausea and two with mild transient anorexia while receiving doses of 250 mg. three times a day. These complaints disappeared with continous administration of the drug. Two receiving diamox complained of mild transient anorexia (Table 2). There were no apparent changes in the blood pressure of either group of patients. None of the above patients was hypertensive.

Laboratory Changes in Clinic Patients

At the end of the first six week period there were six in Group A and five in Group B with serum sodium concentrations below 140 mEq. and a CO_2 combining capacity below 20 mEq. The degree of serum electrolyte alterations were not of the magnitude that would cause serious concern. There was no demonstrable change in the white blood cell count, hemoglobin or hematocrit (Table 3).

Bioassay of Isobutamide

The results of the studies on electrolyte excretion in a metabolic ward are presented in Table 4. The acute effects that Isobutamide had on elec-

TABLE V—EFFECT OF CONTINUOUS DAILY ADMINISTRATION OF ISOBUTAMIDE ON SODIUM AND POTASSIUM EXCRETION

(Sodium Intake = 50 mEq/24 hours)

Day of Drug Administration	Electrolyte Excretion			
	Patient E. M.		Patient L. N.	
	Na	K	Na	K
Control (Average for 3 days)	40	50	43	64
1	93	92	70	93
2	82	84	64	96
3	68	88	68	98
4	64	76	60	81
5	56	68	65	80
6	58	69	60	70
7	46	48	59	80
8	50	56	50	60
9	43	54	60	64
10	48	43	48	69
11	44	58	50	71
12	42	40	48	48
13	40	56	43	50
14	43	51	40	49
15	36	57	38	64
16	44	49	36	58
17	41	50	40	68
18	50	56	44	60
19	46	50	39	53
20	51	59	45	50
21	41	61	40	48

trolyte and water excretion in this study are of similar magnitude as those previously observed for the same dose of Diamox (1) and other carbonic anhydrase inhibitors (Table 4).

Twenty-four hour excretion rates of sodium and potassium over a three week period were determined in two patients. When receiving 250 mg. of Isobutamide daily it would appear that refractoriness develops within one week and sodium and potassium diuresis diminishes to approximately the control levels (Table 5). The prolonged maintenance of dry weight with freedom from congestive phenomenon apparently cannot be explained on a persistent natriuresis but there does not appear to be a secondary retention of sodium.

CONCLUSION AND SUMMARY

1. The continuous administration of Isobutamide, a carbonic anhydrase inhibitor, over a six week period maintained a group of cardiac patients free of edema with sustained weight loss. The patients remained free of symptoms and signs of congestive heart failure during this time.

2. It would appear that the weight loss maintained in cardiac patients receiving isobutamide is slightly more than that produced by a similar dose of acetazolamide (Diamox).

3. The bioassay of isobutamide shows similar increases in sodium and water excretion as are observed following administration of Diamox (acetazolamide).

RESUMEN

1. La administración contínua de isobutamida, un inhibidor de la anhidrasa carbónica, por más de seis semanas mantuvo a un grupo de cardiacos, sin edema y con sostenida pérdida de peso. Los enfermos permanecieron libres de síntomas y de signos de insuficiencia cardiaca congestiva durante este tiempo.

2. Parecería que la pérdida de peso sostenida en el enfermo cardiaco que recibe isobutamida, es ligeramente mayor que la dosis similar producida por la acetazolamida (Diamox).

3. El bioensayo de isobutamida, demuestra similares aumentos de excreción de sodio y de agua, como los observados en la administración de Diamox.

RESUME

1. L'administration continue par voie bucalle d'isobutamide, un inhibiteur de l'anhydrase carbonique, pendant une période de six semaines a permis à un groupe de cardiaques de n'avoir aucun oedème avec une perte de poids appréciable. Les malades restèrent indemnas de symptômes et de signes d'insuffisance cardiaque pendant ce temps.

2. Il semblerait que la perte de poids maintenue chez les malades cardiaques reçevant de l'isobutamide est légèrement plus élevée que celle produite par une dose semblable d'acétazolamide (Diamox).

3. Le dosage biochimique de l'isobutamide montre l'augmentation des éliminations d'eau et de sodium semblables à celles qui sont observées après administration de Diamox (acétazolamide).

ZUSAMMENFASSUNG

1. Die kontinuierliche Verordnung von Isobutamid, einem Kohlensäure-Anhydrase-Hemmstoff, in einem Zeitraum von 6 Wochen hielt eine Gruppe Herzkranker frei von Oedemen mit anhaltender Gewichtsabnahme. Die Kranken blieben während dieser Zeit symptomenfrei und ohne Anzeichen eines Herzversagens durch Stauung.

2. Es hat den Anschein, als ob die Gewichtsabnahme, die sich bei mit Isobutamid behandelten Patienten aufrecht erhalten lässt, etwas höher liegt als diejenige, die man mit ähnlichen Mengen von Diamox erzielte.

3. Die Prüfung von Isobutamid am lebenden Tier ergibt einen ähnlichen Anstieg der Natrium- und Wasser-Ausscheidung wie sie nach Verwendung von Diamox beobachtet wird.

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Ventricular Septal Defect: A Review

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Henri Roger, in 1879, was the first to accurately describe the clinical manifestations of ventricular septal defect, and the term "maladie de Roger" is often used in connection with these malformations. The lesion and the problems associated with it have attracted a great deal of attention in recent years, particularly with the advent of open heart surgery and a means for affecting a cure.

Embryology of The Ventricular Septum—

The septum develops between the fourth and seventh weeks of gestational life.[1] At the end of the fourth week a median partition begins to project inward from the base of the common ventricle. This septum is brought into existence by the enlargement of the future halves of the ventricle on either side of it, and increases in height proportionately as the ventricular sacs become deeper. The anterior part of the septum is derived from a union of the ventral atrioventricular cushion, a local endocardial thickening, with this muscular septum below, and the right and left conus ridges from above. The posterior septum arises from the posterior atrioventricular cushion and the portion of the muscular septum that arises from the apical and dorsal walls of the embryo.[2] The central points of fusion of these regions occurs at the pars membranacea. The anlagen of this part of the septum are a matter of dispute.

Classification of Ventricular Septal Defects—

Defects of the septum may involve regions of the septum related to either the outflow or inflow tracts.[3, 4] The outflow portion of the right ventricle lies between the pulmonary valve above and the nearest part of the tricuspid valve below. Defects in this region are all spoken of as high defects. The inflow tract lies posterior and caudal to the outflow tract.

The outflow tract of the right side of the ventricular septum is divided into superior and inferior regions by the crista supraventricularis. This muscular ridge lies on the floor of the right ventricle between the papillary muscle of the conus below and posteriorly, and the pulmonary valve above and anteriorly. The lesions inferior to the crista represent the most common site for ventricular septal defects, and anatomically lie just below the aortic valve cusps. This is generally spoken of as a membranous ventricular septal defect, but in most cases Becu et al[3] found that the defect involved little or none of the membranous septum, but that the size of the defect was mainly related to the muscular part of the septum that was malformed.

The lesions superior to the crista are closely related to the pulmonary valve whose tissue forms their upper border. The membranous septum is generally intact.

Also known as high defects are those lesions in the upper or basal portion of the septum that are in close relation to the mitral and tricuspid valves.

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The last group, known as low defects, lie in the muscular septum near the apex and are of the type originally described by Roger. Their chief characteristic is the lack of close relationship to any of the valves.

Incidence—

Statistics of incidence are difficult to evaluate since an autopsy series implies some degree of selection, and a clinical series leaves some element of doubt in the absence of absolute anatomic proof.

In several large autopsy and clinical series of congenital heart disease, isolated ventricular septal defect represented 5.5 per cent[5] to 21 per cent[6] of cases studied. These series place the defect as either the first or second most common lesion.

This lesion has been found complicating other cardiac anomolies in 22 per cent[5] and 30 per cent[6] of cases in two series.

Males and females appear to be affected equally.[3, 7]

Diagnosis—

A. History—

The average patient has one or more symptoms attributable to his condition, fatigue, shortness of breath, and retarded growth and development being the most common.[7] Pneumonia, transient cardiac failure, or transient cyanosis are often found somewhere in the past history, as to a lesser degree are chest pain and chronic cough. Least frequent are hemoptysis, syncope, and paroxysms of rapid heart action.

B. Physical Examination—

1) Murmur—This of course is the classical sign. In most cases[7] it is systolic alone, heard along the left sternal border, but heard best in the third and fourth interspaces. It radiates widely. The quality of the murmur varies greatly. It may be harsh and low-pitched or blowing and high pitched. The intensity varies from faint to very loud.

A diastolic murmur may also be heard, rarely alone, but most often in combination with the systolic murmur. It may be early or mid-diastolic, the former heard along the left sternal border, and the latter at the apex.

The systolic murmur is probably due to blood flow through the defect. Its character, location, and transmission depend on many factors: a) Size and exact location of the defect, b) Magnitude of flow and systolic pressure gradient between the ventricles, c) The degree of pulmonary resistance, and d) The degree of rotation of the heart secondary to right ventricular hypertrophy.[7]

The early diastolic murmur may represent functional pulmonic insufficiency as a result of dilatation of the pulmonary valve ring secondary to increased pulmonary blood flow. This theory is supported by the fact that most patients with the early diastolic murmur also have significant pulmonary hypertension.[7] Another theory holds that the murmur may result from aortic insufficiency owing to inadequate support of the aortic valve cusps because of the septal defect.[14]

The mid-diastolic murmur at the apex is interpreted as representing functional mitral stenosis as a result of greatly increased blood flow through a normal valve orifice. Dilatation of the left ventricular cavity with rapid filling may also be a factor.[14]

2) Systolic Thrill—There is no diastolic thrill.

3) The second sound at the base to the left of the sternum is often accentuated, and its intensity correlates roughly with the degree of pulmonary hypertension.

4) Thoracic Asymetry—The left anterior chest may be more prominent than the right.

5) Cardiac Enlargement.

6) Visible Precordial Heave.

7) Cyanosis and Clubbing—Occasionally present, but never marked.

C. X-Ray Examination—

The normal fetal circulation involves a shunt, albeit right-to-left, between the pulmonary and systemic circuits through the ductus arteriosus. The addition of another shunt at the ventricular level of the fetal heart will still, as a rule, allow for an adequate fetal circulation. If, because of the defect, the heart grossly fails to sustain the circulation, intrauterine death supervenes. Thus, Wittenbourg and Neuhauser[8] feel that most infants begin life with a heart of approximately the same external dimensions and that at or shortly after birth, the x-ray will fail to distinguish between a normal heart and the majority of hearts having congenital lesions.

In patients beyond infancy having small defects, with only a small left-to-right shunt, and without pulmonary hypertension, the heart may be normal in size and configuration. With an increase in the size of the lesion and magnitude of the shunt there will be an abnormal load on both ventricles, but x-ray evidence of the lesion is first recognized as right ventricular enlargement. Both ventricles increase in size, but the right ventricle is probably more distensible and enlarges first. The left ventricle enlarges to a considerable degree before there is x-ray evidence of it.[8]

In patients with larger defects the picture may be a changing one which mirrors the progression of the disease. Initially the heart as a whole will be enlarged. In the patient with a large left-to-right shunt this will be predominantly left ventricular, manifested by rounding of the apex and its displacement posteriorly and downward. In the latest stages of the disease, with marked pulmonary hypertension, there will be evidence of enlargement of both ventricles, often with dominance of the right. Normally the right ventricle does not add much to the transverse diameter of the heart, but the hypertrophic ventricle, because of its antero-inferior position, alters the contour of the heart in the postero-anterior film by elevating the left ventricle in a counterclockwise fashion thus elevating the apex, and by increasing the transverse diameter, including the right border, with some increased convexity on this side. As most of the increase in size of the right ventricle is from front to back, both oblique views will show the forward bulge of the anterior contour of the heart encroaching on the retro-sternal space.[8]

In some instances there will be enlargement of the left atrium.[14]

As the disease progresses there will be enlargement of the main pulmonary artery segment and increased vascularity of the peripheral lung fields.[14]

D. Electrocardiogram—

The EKG is of some diagnostic aid, and of significance in establishing the magnitude of the physiologic abnormality, with which it correlates reasonably well.

A normal EKG in a patient with auscultatory evidence of septal defect indicates, if the lesion is truly present, an absence of significant pulmonary hypertension and of significant increase in pulmonary blood flow.

The presence of high amplitude equiphasic QRS complexes in the mid-precordial positions is said to be characteristic of, though not specific for, ventricular septal defect, and has been interpreted as left and right ventricular hypertrophy.[9, 14] A definite left ventricular hypertrophy pattern has been associated with large left-to-right shunts in the absence of severe pulmonary hypertension. This is in accord with the concept that the left ventricle is subject to a greater work load than the right in the presence of a left-to-right shunt at the ventricular level.[14] As the volume of the shunt becomes small or disappears in the presence of severe pulmonary hypertension, there is less evidence of left sided hypertrophy, and a right ventricular hypertrophy pattern becomes dominant. This finding suggests a late stage in the natural history of the disease.[14]

Evidence of atrial enlargement is not common in the EKG.

Evidence of conduction defects is not too frequent, but certainly does occur, and ranges from right bundle branch block to varying degrees of atrio-ventricular block.[7, 9, 14] Although no investigation has been made into the course of the conduction system in hearts with ventricular septal defects, Kirklin et al.[4] feel clinically that it is probably the same as in normal hearts. Thus, there may be a close relation of the Bundle of His and its right and left branches to those defects that appear in the outflow tract of the right ventricle inferior to the crista supra-ventricularis. Those defects that lie superior to the crista and immediately inferior to the pulmonic valve, as well as defects located in the apex of the septum, are not closely related to the Bundle of His and its branches.

E. Cardiac Catheterization—

Once again the findings will vary with the stage of the disease process, but qualitatively if not quantitatively, the results will point more specifically towards ventricular septal defect. Occasionally however, it is difficult to distinguish between this lesion and patent ductus arteriosus, persistent ostium atrio-ventriculare communis, persistent truncus arteriosus, and a single ventricle. Diagnostic information comes chiefly from determinations of pressure and oxygen content in the chambers of the right heart and pulmonary artery. Rarely the catheter will pass through the defect and into the left heart or aorta.

A left-to-right shunt at the ventricular level is present if the oxygen content of blood from the right ventricle is one volume per cent or more than that of the right atrium. When a shunt is only left-to-right, the peripheral arterial oxygen saturation should be normal.

In some cases,[7] the left-to-right shunt may appear to be at the atrial level, i.e. there is an increase of more than two volumes per cent from the venae cavae to the atrium without further rise in the ventricle. All the cases in this series were later conclusively shown to have only ventricular septal defect, and most were characterized by having identical pulmonary

and systemic systolic pressures. The probable explanation therefore is that there was tricuspid incompetence, allowing for a shunt from the left ventricle directly into the right atrium. Obviously this finding complicates the differential diagnosis, and the patient may be subjected to surgery for an atrial septal defect.

The most significant pressure finding is an increase in right ventricular systolic pressure. This may be minimal in the small defects, or, in the larger ones with severe pulmonary hypertension it may equal the systemic systolic pressure. The diastolic pressure tends to be normal or only slightly elevated.[18] In no instance should there be a significant gradient in pressure between the right ventricle and the pulmonary artery, as this would indicate pulmonic stenosis and a probable Tetralogy of Fallot.

Pulmonary artery wedge pressures are generally normal.[10]

Equalization of right and left ventricular pressures, and pulmonic and aortic pressures with a decreased peripheral oxygen saturation, suggests a large ventricular septal defect with a right-to-left shunt.[11]

F. Contrast Roentgenologic Techniques—

These methods are almost never of value in demonstrating the presence of a ventricular septal defect.

Angio-cardiography is of value only for right-to-left shunts, and therefore is suitable only where there is reversal of flow through the defect.

Retrograde aortography is of value in the differential diagnosis to exclude lesions such as patent ductus arteriosus, and aortic or atrial septal defects.

G. Indicator-Dilution Curves—

This technique is based on the theory that the dilution of an indicator substance by the blood stream during its initial passage through the central circulation proceeds in a manner determined by several hemodynamic variables. These include, among other things, the velocity, volume, and pathway of the circulating blood.[13] The actual technique involves intra-venous injection of the dye, and then recording from a peripheral artery the varying concentrations of the dye in the arterial blood.

When of sufficient magnitude, a centrally located left-to-right shunt produces an alteration in the dye-dilution pattern which is characterized by:

1. An appearance time and buildup time of normal duration.
2. An initial peak of concentration of dye that is lower than would be anticipated in a normal person for the amount of dye injected.
3. A prolongation of the disappearance slope of the curve.
4. The absence of the normal secondary peak of dye concentration due to systemic recirculation of dyed blood.

Presumably these alterations are due to central recirculation and to arterio-venous admixture.[13]

Braunwald et al.[12] suggest a similar technique, but inject the dye through a catheter directly into the left ventricle, left atrium, and aorta, and by determining the chamber in which the dye pattern becomes abnormal, they can localize the shunt.

The dye-dilution methods do not seem to be in any way superior to catheterization studies, and in several respects are less reliable. The

limitations include: a) Wide variability in contour of the curve in normal subjects; b) Left-to-right shunts of small magnitude cause only minor, and perhaps unrecognizable abnormalities; c) Without introducing the dye by catheter it is not possible to predict the anatomic location of the defect.[13]

H. Nitrous Oxide Test—

Grant et al.[15] have devised this test in lieu of certain shortcomings of standard catheterization. They found that large differences in oxygen content of blood from the chambers of the right heart may be normal, and even multiple samples from a single chamber may vary widely. Owing to this, the diagnosis of a shunt into the right ventricle or pulmonary artery requires an increase in oxygen content of at least one volume per cent, and therefore small shunts may be missed.

The nitrous oxide test is performed during right heart catheterization. After a sample of blood has been drawn for nitrogen blank determination, the patient breaths a mixture of 15 per cent nitrous oxide and air for one minute. During this time blood samples are drawn simultaneously from the right heart and femoral artery, and analyzed for the gas. Nitrous oxide is a soluble inert gas, and is used for the test because of the wide arterio-venous difference that exists during the first minute of its administration. The arterial level rises quickly while the venous level lags because of absorption by the tissues.

In the presence of a left-to-right shunt, left heart blood rich in nitrous oxide increases the nitrous oxide content of right heart blood. Because the arterial level is so variable, the nitrous oxide content of the right heart is expressed as a percentage of the arterial content—the nitrous oxide ratio. A left-to-right shunt is present if this ratio in the right ventricle or pulmonary artery exceeds 20 per cent, or if it exceeds 30 per cent in the right atrium.

Hemodynamics—

A. Flow Through the Defect—

Flow through a defect, both in magnitude and direction, depends on its size and on resistance to the movement of the blood. Normally, pulmonary resistance is low, being only15-20 per cent that of the systemic circuit.[7] Since, for an adequate circulation, left and right sided output must be equal, it follows that the force of contraction of the left ventricle must be greater than that of the right. Therefore, a communication between the two ventricles will favor a left-to-right shunt. If the defect is small, relatively little blood may be shunted because the remaining septum offers greater resistance to flow than does the peripheral arterial circulation. A larger defect on the other hand means less septal resistance and more blood shunted.

Downing and Goldberg[7] point out that with increasing pulmonary resistance, pressure in the right ventricle gradually increases, and as right heart pressure increases, the magnitude of the left-to-right shunt must decrease. The resistance becomes progressively greater, and eventually a state of balance is reached in which, resistance in both circuits being equal under basal conditions, there is no appreciable flow through the

defect. With activity and increased demand there may be a slight shunt in either direction. Even at degrees of resistance less than this a right-to-left shunt may occur under stress, accounting for the transient cyanosis seen in patients with a wide difference between pulmonary and systemic pressures. Ultimately, however, resistance to pulmonary flow becomes greater than resistance to systemic flow and a persistent right-to-left shunt develops, with the appearance of cyanosis. Pulmonary artery pressure does not then mirror pulmonary resistance because the septal defect now acts as an escape vent. Thus, there may develop the clinical features of an Eisenmenger Complex.

B. Pulmonary Hypertension—

It has been found by various authors[3, 14, 16] that patients with ventricular septal defect do not generally die in the pediatric age range, i.e. 1 to 15 years. These authors point out that most children with this defect seen at autopsy are less than six months of age. They generally die of left and right sided congestive heart failure with varying degrees of pulmonary congestion and edema, and hepatic enlargement.[3] Lillehei[17] estimates that perhaps as many as 50 per cent die as a result of their defect in the first twelve months of life. The remainder go on to adult life to present with symptoms at a later date. Many of the early deaths, and most of the later symptoms are due, directly or indirectly, to the one progressive element in the disease process—pulmonary hypertension.

In summing up the present state of affairs, Lillehei has aptly pointed out that "patients with ventricular septal defects have, in reality, two diseases. The cardiac lesion is being well handled, but the problem is in the management of the secondary disease—pulmonary hypertension and arteriosclerosis."

Swan et al.[10] feel there are three factors which may control pulmonary artery pressure:

1. Increased resistance to pulmonary flow beyond the pulmonary capillaries, as in mitral stenosis or congestive heart failure. In such an event the pulmonary artery wedge pressure would be increased, but in ventricular septal defect this is characteristically normal, so this mechanism may be excluded.

2. Increased pulmonary flow in the presence of unchanged resistance. This may well be a factor since it has been found that in patients with patent ductus arteriosus and high pulmonary pressures that manual closure of the ductus results in a decrease in pulmonary artery pressure. Swan has found increased pulmonary flow in the 20 patients he studied, and the average proportion of pulmonary flow representing the shunted blood was 50-60 per cent, i.e. pulmonary flow was about double the systemic.

3. Increased pulmonary resistance. Calculations of resistance are based on measurements of pressure and flow (Poiseulle's Law), and the finding of increased pressure means that the observed increase in pulmonary artery pressure must be disproportionately greater than the increase in pulmonary blood flow. These relative alterations in flow and pressure can best be quantitated in terms of resistance, and as indicated earlier, this must be proximal to the pulmonary capillaries. This is undoubtedly the most important factor in the pathogenesis of pulmonary hypertension.

The most widely accepted views as to the cause of this increased resistance are those of Civin and Edwards.[18] In the fetus the distribution of blood from the right ventricle to the lungs on the one hand, and through the ductus arteriosus to the systemic circuit on the other, is largely dependent on the state of the smaller pulmonary vessels, i.e. at the level of these vessels the resistance to flow is similar to that in the systemic circulation. Were resistance to flow in the pulmonary arterial vessels lower than that in the systemic vessels, as is the normal adult condition, blood from the right ventricle would be almost completely distributed to the lungs. Little or no blood would flow through the ductus into the aorta. In a later article[19] they gave substance to this theory by tracing the development of the pulmonary arteries and arterioles in a series of sections from different age levels. They found that in the muscular fetal arteries the lumen of the vessel is less than the transverse diameter of the vessel wall. Most of this thickening was due to hypertrophy of the medial musculature. By the second half of the first month of life this thickening begins to diminish, and by the time the infant reaches six months of age the small arteries have become dilated and resistance to flow is low. They then propose that the pulmonary hypertension seen at birth represents a continuation of the fetal vascular state, and indeed they have demonstrated muscular arteries of the fetal type in the lungs of patients dying from Eisenmenger's complex. This they consider to be a compensatory mechanism which permits the patient to remain alive. However, the patient pays a price for this, since the mechanism has pulmonary hypertension as a component part.

Intimal fibrous changes may be present in the pulmonary vessels of older patients and produce further narrowing. These changes seem to arise after the medial changes are evident, and are considered to be a reaction to the traumatic influence of existing pulmonary hypertension. These changes are thought to be progressive and to increase pulmonary resistance even further to a point where it equals or exceeds systemic resistance, producing reversal of shunt and cyanosis.

Clinically, the increased pulmonary artery pressure seen at birth may be minimal or severe. After birth, the pressure may remain stable, increase slowly, or rise rapidly. Where pressure is high initially or rises rapidly an early death is likely.

C. Relation of the Defect to Pulmonary Hypertension—

The size of the defect is obviously of prime importance in the development of pulmonary hypertension. It has been pointed out[14] that in a small lesion the factor limiting pulmonary blood flow is the size of the defect. The resistance regulating the major portion of the pulmonary blood flow is at the ventricular level in contrast to large defects where the limiting factor is the capacity of the pulmonary vascular bed. In accord with this the former group is found to have little pulmonary hypertension.

Warden et al.[2] feel that a factor at least as important in this regard is the precise anatomic relation of the defect to the orifice of the pulmonary artery. They believe that even relatively small defects, wherever they be located, situated so that the shunt of blood from the left ventricle projects directly into the pulmonary artery are hemodynamically more deleterious than considerably larger defects situated so that the left

ventricular jet strikes the opposite right ventricular wall in such a way as to create turbulence in the outflow tract of this ventricle. The consequent increased resistance due to this turbulence, creates, in effect, a functional pulmonic stenosis tending to dampen the physiological consequences of the defect. Most authors[3, 14] believe that this is correct in theory but is not borne out in practice, and that the size of the defect is the sole factor governing the clinical picture.

Relation To Other Complexes—

A. The Eisenmenger Complex—

This is a cyanotic type of congential heart disease comprising a high ventricular septal defect, overriding of the defect by the aorta, pulmonary hypertension, and right ventricular hypertrophy. The only difference between this and isolated septal defect is the overriding aorta and consequent cyanosis. The mal-position of the aorta may range from mere overriding to actual and complete dextraposition. In the former type, Bailey[11] feels that the complex is a misnomer. He states that a simple defect located high in the septum will in any heart give the impression of overriding. Others[14] take a less demanding point of view and feel that when pulmonary hypertension is severe in an isolated defect and reversal of flow through the defect occurs, that there is created a physiologic, albeit not anatomic, overriding of the defect. Thus, this group prefers to think of the Eisenmenger Complex not as an anatomic entity, but rather as a stage in the natural history of an isolated septal defect. It must be pointed out however, that the existence of an anatomic Eisenmenger Complex, i.e. when there is actual dextraposition of the aorta, cannot be denied.

B. The Tetralogy of Fallot—

Gasul et al.[16] in studying a group of 15 infants with ventricular septal defects over a course of several years, have in four cases observed the development of pulmonic stenosis. This change was clinically manifested in all by a diminished second heart sound at the pulmonic area, and in two by the development of the clinical findings of Tetralogy of Fallot.

These authors suggest that the child with ventricular septal defect may protect himself in at least two ways—either through the development of pulmonary hypertension, or in some cases through the development of pulmonic stenosis. They make no estimate as to how many cases go this way, but do feel that if this change is to occur it does so at an early age or not at all.

This is the only report of such a phenomenon this author has seen in the recent literature.

Prognosis Without Surgery—

Most of the work in this paper has been directed toward the commoner class of ventricular septal defects, i.e. those variously situated high in the septum, but mention should also be made of the less common but more benign small defect located low in the septum and unrelated to any valve orifice. This is the lesion referred to as maladie de Roger, and it carries a rather good prognosis. The patients develop almost no pulmonary hypertension, and except for the risk of sub-acute bacterial endocarditis they may expect to live a normal life.

As for the larger, higher defects, Lillehei believes that probably 50 per cent die in the first year of life because of the lesion. Most of these die in left ventricular failure,[14] some probably in conjunction with pulmonary infection. As the remainder of the patients reach adult age and develop progressive pulmonary hypertension, right ventricular failure contributes a rapidly increasing element to this picture. Just how long these patients may live is difficult to say, but this author has rarely read of a patient surviving beyond 55 to 60 years of age.

Sub-acute bacterial endocarditis is a risk that all patients must carry, no matter how large or small the defect. The organisms may implant either on the defect margins, or on the free wall of the right ventricle opposite the defect. Selzer[21] estimates that 25 per cent of patients with this defect develop bacterial endocarditis. Others[3, 7] believe the figure is lower, possibly below 5 per cent.

Selection of Patients for Corrective Surgery—

Lillehei[17] has outlined some criteria for surgery:

1. Infants who fail to gain weight.
2. Infants with recurrent or persistent cardiac decompensation that is resistant to medical therapy.
3. Infants who suffer repeated respiratory infections.

On the other hand, in infants who are gaining weight normally or nearly normally and who appear to be responding well to medical therapy, he prefers to delay corrective surgery till at least 18 months when the child is perhaps better able to withstand major surgery. He feels that waiting longer than this increases the risk, since in some patients the pulmonary artery pressure can double in one year. On the other hand there are some patients whose pulmonary pressures may remain stable for years, however, there is at present no way of telling into which group any given patient will fall.

From a technical aspect early operation is also desirable. Lillehei claims that the defects are nearly always small and easily closed by stitches only. To delay surgery would be technically undesirable since these defects grow in size as the septum grows.

In the adult the selection of surgical patients becomes a great deal more difficult. The chief problem is the existence and degree of pulmonary hypertension. It has been shown that in the presence of severe pulmonary hypertension the operative mortality is markedly increased, and the immediate and prolonged prognosis after surgery are not good. Presumably the pulmonary vascular changes have progressed to a point where they are no longer reversible. The problem may eventually resolve itself into the selection of patients on the basis of lung biopsy. Apparently the state of the pulmonary vessels seen in these sections correlates rather well with operative risk and prognosis.

Surgical Correction—

The most immediately apparent method of therapy for a patient with this lesion is closure of the defect. For many years this was mere phantasy, but in the 1930's Claude Beck opened a new era with the demonstration that the heart could be approached surgically. The barrier had been crossed, and progression toward repair on intra-cardiac lesions was not far off. The technique of closed cardiac surgery however, still was

not satisfactory for repair of ventricular septal defects. The most frank approach, i.e. suturing the edges of the defect, was rarely successful. Blind implantation of sutures was both dangerous and difficult, especially in those defects whose margins lay in close proximity to the aortic valve ring. Alternatives to direct suture were suggested. Bailey[11] favored plugging the defect by pulling a tapered, pedicled, viable pericardial tube through it from the right ventricular side and suturing it to the free wall of the left ventricle, hoping for fibrous union between the tube and the defect margins. However, this and other techniques suggested still fell short of the results anticipated with the ideal "direct" approach. This approach was finally made possible with the advent of open heart surgery.

Surgical correction of the lesion by open cardiotomy is mainly dependent upon the use of either hypothermia or extra-corporeal circulation, the most popular variant of which is the mechanical pump oxygenator. Both techniques are successful, although the pump oxygenator is somewhat more in favor since it allows for longer operations than does hypothermia. There are certain problems inherent in each method, but these are beyond the scope of this paper.

If the heart is beating actively during the cardiotomy air may be aspirated, pass to the left side of the heart and be ejected into the aorta at the next contraction. To avoid this, drugs such as acetyl choline, prostigmine, or potassium citrate are administered via coronary artery perfusion to produce a flaccid heart.

Direct suture may be used in small defects, but in the larger ones it is often followed by partial disruption along the suture line. It is believed that the living ventricular septum allows tight stitches to cut through rather readily. Thus, in the larger lesions, Kirklin[4] recommends the use of a securely anchored polyvinyl-formal (Ivalon) sponge cut to conform to the shape of the defect. Mattress sutures are placed for repair so that they grasp one side of the defect, pass through the sponge, and are then anchored to the other side of the defect. Thus, the sponge helps to fill the tissue defect, and allows a snug repair without the stitches having to be drawn too tightly.

Complications of Surgery—

Some degree of post-operative conduction defect is common,[22] but generally well tolerated. The most serious conduction defect, and the one that is a threat to life is complete heart block. Lillehei[4] estimates the incidence of complete heart block following surgery to be about 12 per cent, probably because in the most frequent location of defects there is a close relation of the conduction system to the area for placement of sutures. He also believes that in patients with severe pulmonary hypertension and diminution of cardiac reserve there is a predisposition to block. This element is difficult to control, but interruption of the conduction pathway by a suture can be guarded against if certain precautions are taken. If, with the placement of a single stitch, complete heart block occurs, Lillehei removes the offending stitch and places it in a slightly different place. If this maneuver is not of value he continues regardless since the primary objective, if the patient is to live, is closure of the defect. He then attempts to correct the condition, if possible, by post-

operative medical therapy with Isuprel, or with the combined use of myocardial electrodes and the artificial pacemaker.[23]

In all age groups, but particularly in children under two years of age, one of the chief factors involved in post-operative morbidity and mortality is the development of respiratory complications.[17] Even normal infants have limited respiratory reserve, but in those infants with large defects and severe pulmonary hypertension the reserve is even further diminished. Thus the management of the secretions that are inevitably retained in their bronchial tree, and the consequent frequent development of pneumonia, becomes a major problem, and one that is as yet unsolved.

Another factor complicating surgery in patients with advanced pulmonary pathology results from the altered hemodynamics following closure of the defect. Some patients will die due to circulatory failure resulting from the high resistance in the pulmonary circuit.[23]

Mortality Rates—

In the largest single series reported on at this time, Lillehei et al.[24] have operated on 154 patients for closure of ventricular septal defects. Their overall martality rate was 29.3 per cent. The figures for specific groups are significant, and are therefore presented:

Pulmonary Hypertension

	Moderate* Per Cent	Severe** Per Cent	Total Per Cent
Under 2 Years of Age	29	48	39
Over 2 Years of Age	6.8	37	24
Total	14	40	—

*Pulmonary artery pressure less than 70 per cent of aortic pressure.
**Pulmonary artery pressure greater than 70 per cent of aortic pressure.

From these data it is evident that the "ideal" group from the standpoint of surgical risk are patients over two years of age, and with only moderate or minimal pulmonary hypertension.

It is also of interest to note that this group found that the type of cardio-pulmonary by-pass used does not seem to have an effect on mortality.

Therapeutic Results—

In catheterization studies done on patients surviving surgery,[24] most patients appear to have a significant decrease in pulmonary artery pressure and blood flow. Some degree of residual shunt is, however, not uncommon.

The various murmurs may or may not disappear. In all likelihood this will depend on the degree of pre-operative cardio-pulmonary aberrations in all parameters, as well as the completeness of closure of the defect.

Adams et al.[22] found that pre-operative growth failure which is so frequently observed, is remedied and nearly all their patients returned to average growth levels post-operatively when the shunt had been closed and pulmonary hypertension was not a prominent feature.

They also found that increased pulmonary vascularity, as estimated by x-ray, soon returns to normal, while the cardiomegaly disappears less strikingly.

In this same series all patients were found post-operatively to have complete or incomplete right bundle branch block.

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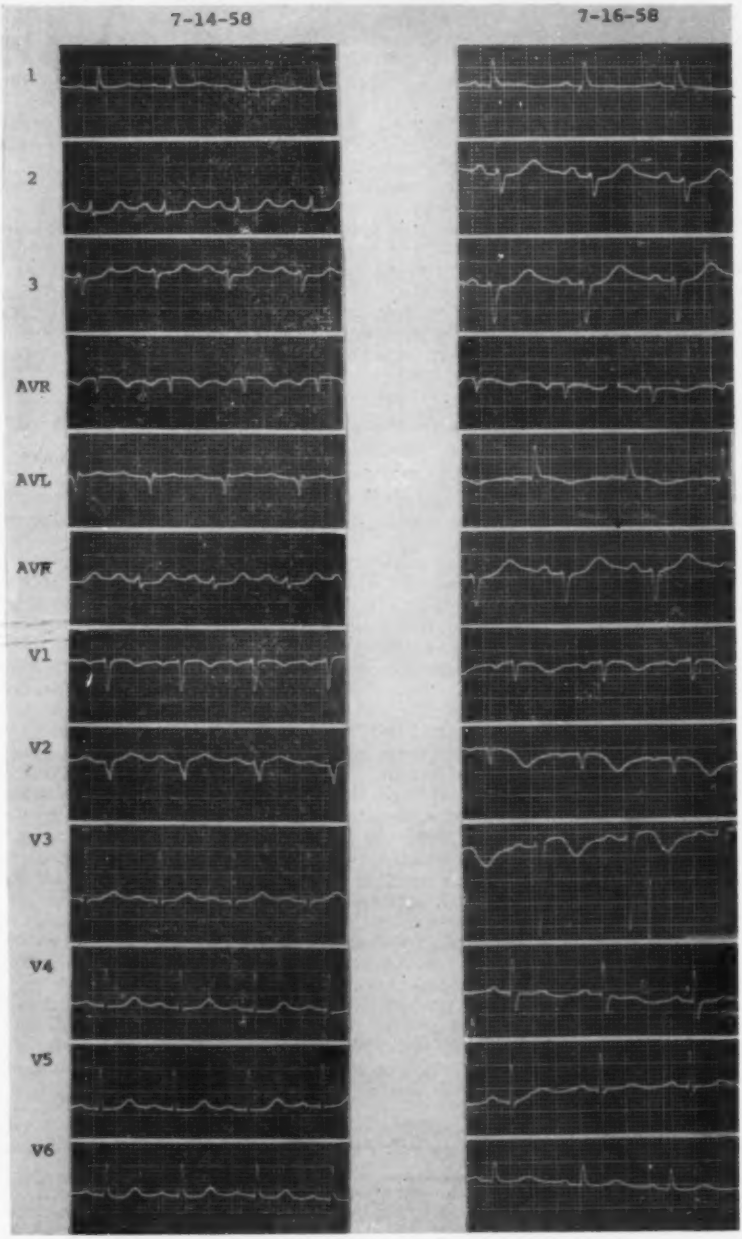
ELECTROCARDIOGRAM OF THE MONTH

The Electrocardiogram of Acute Diffuse Myocarditis



The clinical picture of acute interstitial myocarditis often simulates that of acute myocardial infarction. The record presented below is that of a 59 year old white woman admitted to the hospital July 14, 1958. The distribution of her pain and her clinical course were typical of an acute myocardial infarct.

From the time of admission her blood pressure fell to shock level within 24 hours, necessitating increasing amounts of Levophed by continuous intravenous drip, as well as intravenous hydrocortisone. Serum glutamic-oxalacetic transaminase on July 15, 1958 was 21 units. On July 16, 1958 the Serum glutamic-oxalacetic transaminase rose to 55, and on July 18, 1958 the Serum glutamic-oxalacetic transaminase was 72 units. The remainder of the chemistry and electrolyte profile were within normal limits. Her course was progressively downward, and she died on July 18, 1958.

The first electrocardiogram taken July 14, 1958 was abnormal only because of low voltage. A repeat record taken July 16, 1958 was compatible with anteroseptal ischemia or infarction. Unfortunately, no additional electrocardiogram was obtained until the time of death when it was felt that she died in ventricular fibrillation.

An autopsy revealed an acute diffuse myocarditis of a Fiedler type with marked dilatation of the heart. Sections of the heart were shown to several pathologists, and one remarked that it was unusual that the predominant inflammatory cell was a histiocyte. There were many necrotizing changes in the scattered muscle fibers, as well as inflammation in the epicardial fat in the interstitial fibro-fatty tissue, and in the mural endocardium. Although this may represent a form of viral myocarditis, the concensus of opinion was in favor of diffuse myocarditis of the Fiedler type.

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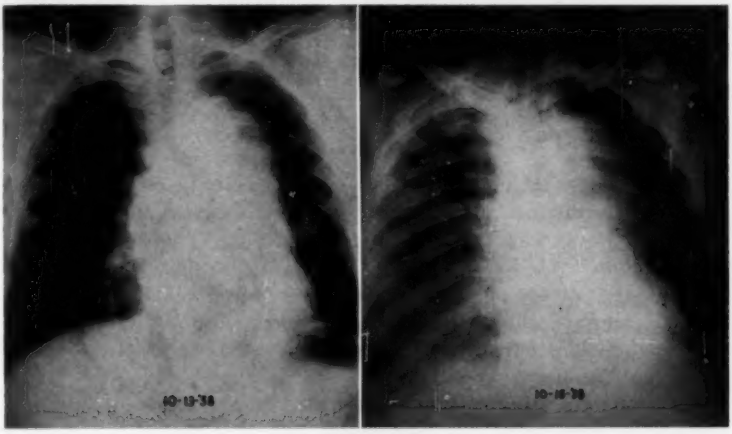
The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

Clinical Information

The patient was a 53 year old white man with a one day history of severe abdominal and thoracic pain that radiated into his neck and left shoulder. He was nauseated and frequently vomited clear fluid. Physical examination was negative.



Diagnosis

Dissecting Aneurysm of the Aorta

Posterior-anterior x-ray film of the chest on October 13, 1958, shows that the lung fields are well aerated and clear. There is diffuse widening of the mediastinum to the left, apparently representing a greatly dilated aorta. The aortic arch presents a smooth, left contour. Below this region the contour of the descending aorta is uneven and not sharp. Recumbent film of the chest two days later demonstrates the presence of a right pleural effusion, with the mediastinal shadow unchanged.

A dissecting aneurysm of the aorta, three times more common in men than women, is not a true aneurysm in that the vessel itself is not actually dilated. Atherosclerosis and hypertension are usually the predisposing factors along with cystic changes in the media of the vessel. Marfan's syndrome may be present. The aneurysm results from a tear of the intima, allowing the blood to dissect its way into the media, separating the inner third of the vessel from its outer two thirds. Dissection can occur both up and down the aorta and may extend into the abdominal aorta. Roentgenograms of the chest often show rapid progressive widening of the mediastinum. If the dissection occurs near the aortic valve, the most frequent site, the right superior mediastinum is usually widened. If it includes the descending aorta or starts below the aortic arch, as in the present case, the left superior mediastinum is generally widened. The mural contour of the aorta in the region of the dissection is often lumpy or irregular. The dissection may terminate either by a breakthrough back into the lumen of the aorta or by external rupture with resultant hemorrhage into the mediastinum, pericardium, or retropleural or pleural spaces, and death. In the present case the right side of the aortic arch ruptured, and blood dissected its way from the mediastinum into the right retropleural and pleural spaces.

The diagnosis of dissecting aneurysm is assured if there is progressive increase in the size of the aorta over a short time interval or, as in this case, the sudden appearance of pleural effusion, indicating rupture of the aneurysm.

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Case Report Section

Ventricular Aneurysm

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Introduction

Aneurysm of the left ventricle has been long recognized as a pathologic entity.[1] The recent growing ability to diagnose and treat the lesion during life has stimulated a new interest in the condition.[2]

Current concepts hold that left ventricular aneurysm may develop days, weeks or months after a myocardial infarction, and that it is more likely encountered when patients are permitted early ambulation.[3] It is now believed aneurysm occurs in as many as 20 per cent of those suffering from coronary occlusive disease.[4]

Anatomically the lesion varies in size and may not be sharply demarcated from the more normal myocardium. The wall generally is quite thin and the endocardial surface may be the site of a mural thrombus.

The essential pathophysiologic result of myocardial aneurysm is reduction in cardiac output. This may occur because of the quantitative loss of contracting muscle tissue. Certain theoretical considerations suggest that in addition the mechanical efficiency of the remaining myocardium is reduced seriously.[5] It also has been claimed that by receiving a portion of the output during systole and returning it to the chamber during diastole the aneurysm ultimately may impose a significant volume load on the left ventricle.[6]

Although there is no characteristic symptom of ventricular aneurysm the pain of coronary artery insufficiency, the manifestations of congestive failure and the indications of embolic accidents are most common.

Although a routine roentgenologic examination of the heart is helpful in establishing a diagnosis, specialized studies including fluoroscopy, roentgenkymography, electrocymography and ventriculography often are required.

The prognosis of patients with myocardial aneurysm basically is that of the underlying coronary artery disease. However, it is considerably influenced by the likelihood of congestive heart failure and peripheral emboli. Accordingly resection of the lesion has been advocated and practised with imposing results.[7-8]

The patient herein reported represents a classical embodiment of many of the views concerning etiology, pathophysiology manifestations and therapy. Of greater importance the case provides additional information pertaining to the pathogenesis of myocardial aneurysm, the variations in its

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clinical expressions and the natural hazards attending its surgical correction.

Case Report

J. M. P., a white man aged 52 was admitted to the Thoracic Surgical Department of the Hahnemann Medical College and Hospital on April 23, 1958.

He suffered an acute myocardial infarction on June 24, 1957 (Fig. 1). He was hospitalized at the Buenos Aires Naval Hospital Argentina, anticoagulated for 20 days, and kept at absolute bed rest for 100 days. Almost at the outset the manifestations of left ventricular failure developed requiring digitalization, a salt poor routine, and the use of oral and injectable diuretics.

The diagnosis of left ventricular aneurysm was made shortly after the acute infarction and was considered responsible for the persistent failure.

At the time of admission to Hahnemann Hospital he was in no acute distress. The blood pressure levels were $\frac{90\text{-}104}{60\text{-}70}$. Normal sinus rhythm was present and was interrupted by an occasional premature ventricular contraction. No murmur was audible. Moist rales were present at each of the lung bases. The liver was palpable a finger below the right costal cage.

On laboratory examination the urine and the complete blood count were normal. The blood urea nitrogen was 10 mg. per cent; the blood sugar was 104 mg. per cent; the total plasma protein 6.6 gm. per cent with the albumin 3.7 gm. per cent and the globulin 2.9 gm. per cent; the chlorides 84.6 mEq.; the sodium 148 mEq. and the potassium 4-5 mEq. The Volmer and VDRL were non-reactive.

Routine roentgenographic study of the heart revealed its size to be increased 3 plus with the left ventricle main involved (Fig. 2). The contour was sabot.

Ventriculogram was performed on May 8, 1958. The technique employed was that described by Lehman[7] (Fig. 3).

The electrocardiogram of April 23, 1958 is seen in Figure 4, A and B. This pattern remained constant during the entire hospital stay. It was considered suggestive of anteroseptal infarction.

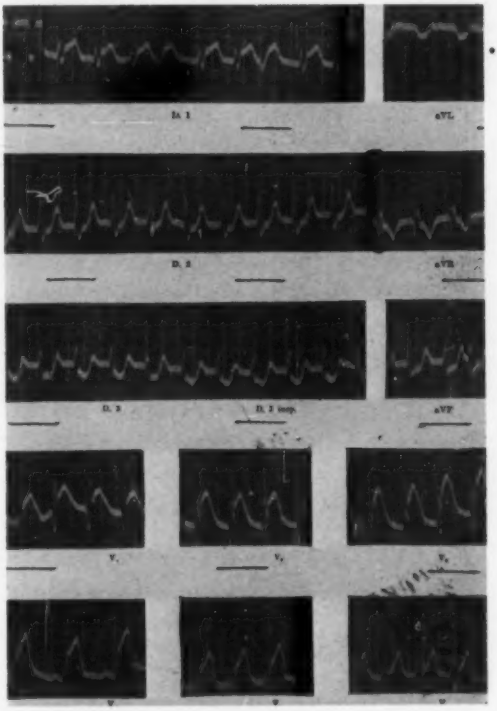

FIGURE 1: The electrocardiographic pattern of an acute antero septal myocardial infarction obtained within the first 24 hours of onset of pain.

FIGURE 2A

FIGURE 2B

Figure 2A: The posterior antero-lateral view of the heart revealing the *sabot* contour, and the plus 3 enlargement of the left ventricle.—*Figure 2B:* The right oblique view showing concomitant enlargement of the left atrium.

The complete clinical review was considered diagnostic of a left ventricular aneurysm. Because it was believed that the lesion contributed materially to the presence of the disability and heart failure, resection of the ventricular aneurysm was advised.

Surgery was performed on May 13, 1958. During the repair of the myocardium, after resection of the aneurysm, cardiac arrest occurred. Although sinus rhythm was restored for a period of time death finally ensued.

The gross specimen consisted of three pieces of tissue. The first piece was a considerably tortuous membraneous tissue, measuring 7.5 cm. in greatest dimension. Thickness was 0.5 to 2.0 cm. including the fatty tissue. The second tissue measured

FIGURE 3A

FIGURE 3B

Figure 3A: Direct opacification of the left ventricle showing filling of the aneurysmal sac 4 seconds after the initial injection of dye.—*Figure 3B:* Ventriculogram 6 seconds after injection of dye.

5 cm. in greatest dimension and presented a regular plate-like appearance. The thickness of this tissue was 0.8 to 1.5 cm. The third specimen presented thick membrane 7 cm. in greatest dimension.

The microscopic sections consisted of rather acellular, dense, fibrous tissue characterized by rather extensive areas of hemorrhage. One surface was covered by fatty tissue, the other surface was composed of a fibrous tissue. There was no cardiac muscle recognizable in the section.

Discussion

The left ventricular aneurysm in this patient developed within days of an anteroseptal myocardial infarction. Since early ambulation was not permitted the pathogenesis must have been related to the size of the infarction and the stretching effect of the intra-cavity tension on the extensive area of inelastic necrotic muscle tissue. This combination of physical events unquestionably is the critical issue in the formation of all myocardial aneurysms. The degree to which early ambulation adversely influences this relationship remains unknown.

It is quite clear from the present report that congestive failure arising from a myocardial aneurysm is apt to be refractory in spite of carefully regulated therapy. Viewed differently the persistence of failure following an infarction should suggest the possibility of complicating aneurysm.

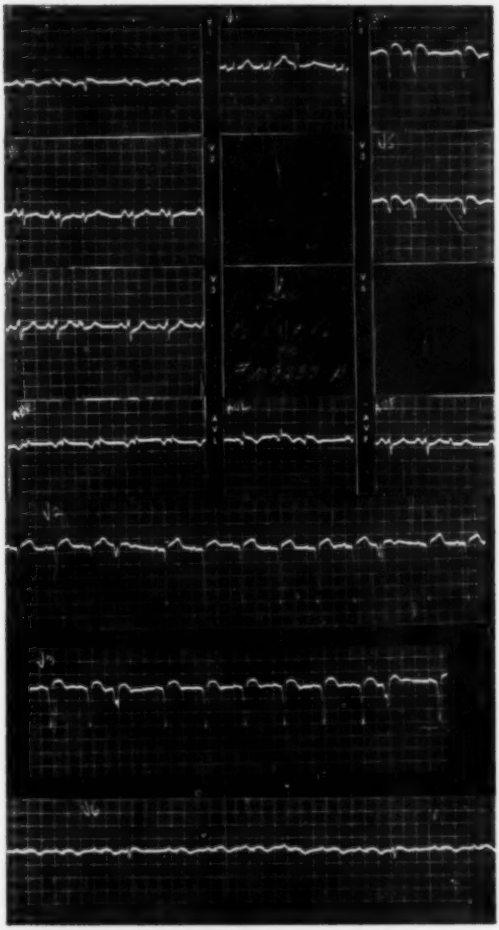

FIG. 4A

FIG. 4B

Figure 4, A and *B:* The electrocardiogram approximately 1 year after initial myocardial infarction indicating extensive antero septal damage.

It is particularly noteworthy that the more complicated roentgenographic methods failed in this patient to delineate the aneurysm more satisfactorily than the routine type of examination. Nevertheless it is proper to state that ventriculography is a particularly effective method of visualizing an aneurysm provided the cavity is not occluded by thrombus. Although the risk of this type of study in patients with advanced coronary occlusive disease readily is acknowledged it is not of a magnitude to preclude the investigation.

The fundamental surgical techniques utilized in the correction of a ventricular aneurysm consists of the tangential excision of the sac utilizing a special clamp across the base of the lesion. The mortality rate for the procedure without the use of a partial bypass has been reported.[7, 8] The surgical interference is predicated upon the ability to excise the aneurysm and restore the continuity of the left ventricle so that it functions as efficiently as the basic coronary artery disease will permit. However, well tolerated in the group of patients recorded in the literature thus far death may occur from cardiac arrest or from peripheral emboli. The latter may develop wherever intra-cavity thrombotic material is dislodged. The effectiveness of the procedure in restoring a modicum of health in critically afflicted patients is born out by the fact that a survival of three years after surgery has been recorded.[9]

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A Case of Extra-Pulmonary Tuberculosis with Hemorrhagic Manifestations*

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The occurrence of extra-pulmonary tuberculosis in the absence of clinically demonstrable evidence of pulmonary involvement is well known. The diagnosis of such cases is often difficult, because of the paucity of characteristic findings. The disease may present itself in a variety of ways, and this has prompted us to report a case in which hemorrhagic manifestations were the outstanding features.

W. M. S., a 21 year old negress was admitted to the Gynecological Service of Kings County Hospital on March 18, 1949, with complaints of menorrhagia and metrorrhagia of seven years duration. Menstruation, which had begun at age 14 was always irregular, and the flow would last 14 to 21 days. For three weeks prior to admission, vaginal

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bleeding had increased in severity, causing her to seek hospitalization. She denied all other symptoms, and specifically gave no history of bleeding from cutaneous or mucosal surfaces. There was no family history of blood dyscrasia.

The abnormal physical findings were limited to the abdomen and pelvis. Minimal, bilateral, lower quadrant tenderness was present, unaccompanied by rigidity, rebound, or areas of point tenderness. No viscera or masses were palpable abdominally. A pelvic examination revealed a tender, cystic mass, in the left lateral fornix.

The admission laboratory studies revealed hemoglobin of 8.6 Gm. per cent, hypochromic-microcytic erythrocytes, and white blood cell count of 9,720 per cu. mm., consisting of 50 per cent neutrophils, 40 per cent lymphocytes, and 2 per cent monocytes. Two sickle-cell preparations were negative.

A diagnosis of tubal pregnancy was entertained, however surgical intervention was postponed because of the spontaneous onset of severe bleeding from the nose and gingiva. An hematological investigation revealed the following abnormalities; bleeding time over 10 minutes, platelet count of 8,000 per cu. mm., positive tourniquet test and no clot retraction in 24 hours. Bone-marrow aspiration revealed normoblastic; megakaryocytes were present, but no platelets were seen. A diagnosis of idiopathic thrombocytopenic purpura was made, and on March 28 splenectomy was performed because of continued severe bleeding from the nose, mouth and uterus. The histopathologic report was acute tuberculous splenitis, with caseous tuberculosis of the adjacent lymph nodes.

Following splenectomy, the bleeding ceased dramatically, and no abnormality of the clotting mechanism could be detected. Repeated x-ray chest films, sputum and gastric examinations for tubercle bacilli were negative. She was placed on dihydrostreptomycin, 0.5 Gm. daily for seven weeks, when (June 3, 1949), she left the hospital against advice.

The patient was readmitted to the Gynecological Service on December 31, 1955 because of bilateral, lower quadrant, abdominal pain of one weeks duration. Her menses had ceased suddenly in 1953, and from that time she had noticed increasing weakness and loss of 50 pounds in weight. She had no medical care since her last admission, six years previously.

The physical examination showed her severely and chronically ill. The abnormal findings were still limited to the abdomen and pelvis. There was generalized abdominal tenderness, with no rigidity or rebound tenderness. A moderate amount of white, vaginal discharge was observed, and both fornices were indurated, thickened and tender. The cervix and uterus were not remarkable.

She ran a septic course, with temperature elevations to 104° F. unresponsive to 1.2 million units of penicillin, 1.0 Gm. of streptomycin, 300.0 mg. of iso-nicotinic acid hydrazide (INH) and 12.0 Gm. of para-aminosalicylic acid (PAS) daily. Roentgenograms of the chest and abdomen were normal. The sputum, gastric aspirate, feces and vaginal discharge revealed no tubercle bacilli. Eight days after admission, bleeding from the external os of the cervix was observed. Blood studies then indicated hemoglobin of 8.5 Gm. per cent white blood cell count of 23,000 per cu. mm. (neutrophils 88 per cent, lymphocytes 9 per cent, monocytes 3 per cent), platelet count of 200,000 per cu. mm., bleeding time of 2 minutes, clotting time 5 minutes, negative tourniquet test, total serum bilirubin of 0.3 mg. per cent and negative sickle-cell preparations. Severe vaginal bleeding continued and laparotomy was performed on January 9, 1956.

On opening the abdomen, the peritoneum appeared thickened and edematous. The entire small bowel was encapsulated with a red, coarse, fibrinous material. The pelvic viscera were covered with a similar exudate, and bilateral tubo-ovarian abscesses were present, adherent to the small and large intestine and posterior pelvic wall. Subtotal hysterectomy and bilateral salpingo-oophorectomy were carried out. The pathological report was tuberculosis of the ovaries, fallopian tubes, uterus and omentum.

The patient did well post-operatively until January 17, when bleeding from the vagina, nose, mouth and rectum suddenly began. Investigation revealed hemoglobin of 6.5 Gm. per cent, red blood cell count of 2.57 million per cu. mm., mean corpuscular volume of 101 cu. microns, mean corpuscular hemoglobin concentration of 33 per cent, mean corpuscular hemoglobin of 33 micro-micrograms, white blood cell count of 13,050 per cu. mm. with 70 per cent neutrophils, 28 per cent lymphocytes and 2 per cent monocytes, reticulocyte count of 3.6 per cent, platelet count of 215,670 per cu. mm., bleeding time of five minutes, clotting time of 14 minutes, complete clot retraction in two hours and 45 minutes, prothrombin time of 17 seconds (control 13 seconds) and prothrombin consumption time of 36 seconds. The bone-marrow showed a normoblastic hyperplasia, with adequate megakaryocytes and platelets. It was felt that the bleeding was due to a defect in the early phase of the clotting mechanism. During a 20 day period (January 17 to February 6), she received 35 units of whole blood, 1,000 cc. of fresh frozen plasma, 2.8 Gm. of fibrinogen, as well as 50.0 mg. of vitamin K_1 twice daily and one teaspoon of bio-flavinoids four times daily. Bleeding from the vagina and nose subsided, but rectal bleeding continued. A proctoscopic examination revealed several shallow ulcerations of the rectal mucosa, measuring 1 to 2 cm. in di-

ameter. On February 6, transverse colostomy was done in an attempt to control the rectal hemorrhage. At operation the bowel was studded with yellow tubercles, and numerous, dense adhesions were noted. The microscopic examination of the peritoneal and omental tissues revealed fibrous, granulomatous inflammation consistent with tuberculosis; the colonic mucosa appeared free of disease.

Following the colostomy, she was transferred to the Tuberculosis Division, where streptomycin, INH, and PAS were administered. Spontaneous bleeding did not recur, and she improved steadily, gaining 45 pounds during hospitalization. Chest x-ray films taken at monthly intervals revealed no pulmonary or pleural disease (figure 1). Radiographic studies of the small bowel and colon were also normal. Repeated examinations of sputum, urine, stool, gastric washing and bone-marrow aspirates were negative for tubercle bacilli. The colostomy was closed after having functioned effectively for one year, and she was discharged apparently cured, after 12 months on the tuberculosis service, to continue on INH and PAS.

COMMENT

The association of purpura with tuberculosis has been well documented. Garin[1] in 1920, reviewed the literature and collected 26 such cases. In the majority of these cases, the blood studies were too incomplete to enable an exact diagnosis of the deranged, clotting mechanism involved. Villa[2] in 1928, was the first to report thrombocytopenic purpura in a patient who at autopsy was found to have disseminated miliary tuberculosis. Since that time six additional reports have appeared.[3-7]

The early writers considered purpura to be a critical manifestation of acute disseminated miliary tuberculosis. Pratsicas[8] found extensive dissemination in necropsy material of four patients who died of tuberculosis, and who had had purpuric manifestations before death. Reitano,[9] in a review of the subject, studied 11 cases and concluded that purpura in miliary tuberculosis was not an infrequent phenomenon, and that it represented an acute symptom, observed in many forms of septicemia. A more comprehensive view was taken by Ellman and Johnson,[6] who, in a study of the more recent literature found that purpura had been associated with all forms of tuberculosis, both pulmonary and extra-pulmonary.

Attention to tuberculosis of the spleen as a possible cause of purpura was pointed out by Winternitz.[10] He defined splenic tuberculosis as a condition in which the dominant signs of the tuberculous process occurred in the spleen, with no clinically demonstrable evidence of tuberculosis elsewhere. Fifty-one such cases were collected,

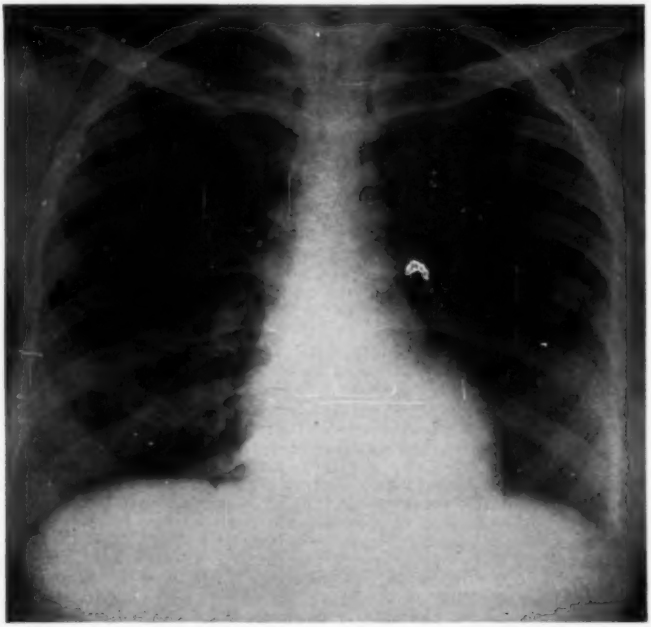

FIGURE 1: No evidence of pulmonary or pleural disease. Cardiac silhouette normal.

two of which exhibited cutaneous purpura. That the spleen may on occasion be a major factor in the production of the bleeding disorder cannot be doubted. Several reports of splenectomy for idiopathic thrombocytopenic purpura with apparent cure have appeared, and microscopic examination of the removed spleens revealed tuberculous involvement.[3, 4, 6, 7]

It seems equally certain that in many cases the spleen plays an insignificant role. Tuberculosis of the spleen unassociated with bleeding tendency has been reported.[11-13] Conversely, purpura has occurred in patients with little or no tuberculous involvement of the spleen.[1, 8, 13] Several theories as to the pathogenesis of the purpura have been advanced. Cannata[14] suggested that adrenal insufficiency with consequent loss of vascular tone was a major factor. Bauch[15] concluded that tubercle bacilli or their toxins acted as irritants to the endothelium of the cutaneous vessels and produced purpuric spots. Pratsicas[8] felt that the purpura was due to cutaneous emboli in the course of tuberculous bacillemia. Gouley et al,[5] and Kalinowski and Walker[7] found extensive involvement of the bone-marrow to be a prominent factor. In a review of the subject, Ellman and Johnson[6] concluded that the purpura was produced in one of three ways; hypersplenism, infiltration or depression of the bone-marrow, or allergy to tuberculoprotein resulting in thrombocytopenic purpura or anaphylactoid purpura.

The case which we have reported suggests that several factors are involved in the pathogenesis of the hemorrhagic manifestations of tuberculosis. That the spleen does play a role is evidenced by the dramatic response of the patient to splenectomy, and the subsequent absence of spontaneous bleeding for a period of six years. The recurrence of bleeding at the end of this time and in the absence of demonstrable abnormalities of the clotting mechanism was not explained. There was abundant evidence of widespread, active tuberculosis within the abdominal cavity, and from this one could postulate that either allergy, bacillemia, or bone-marrow involvement were responsible.

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Intralobar Pulmonary Sequestration*

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Intralobar pulmonary sequestration is a developmental anomaly in which a portion of developing lung tissue receives an independent blood supply from the aorta, usually immediately above or below the diaphragm. This sequestrated portion of lung is non-functioning and develops cystic changes. Wall[7] found three cases in 385 thoracotomies pre-operatively on clinical and roentgenographic findings.

Case Report

A. T., a 16 year-old Puerto Rican girl was admitted to the hospital with complaints of productive cough for three weeks, recent hemoptysis and weakness. She stated that she was very prone to upper respiratory infections and every winter she had had numerous "colds." Three weeks prior to admission she developed a cough which was non-productive initially. In the week prior to admission she had expectoration of bright red and dark blood, associated with right chest pain. Physical examination revealed slight dullness at the right axilla without other abnormal findings. Her temperature was 98°, puise 70, blood pressure 120/70, and vital capacity 3,000 cc. The sputum was negative for acid fast bacilli or other pathogenic organisms on smear and culture. The erythrocyte count was 4,300,000; white blood cells 6,800; hemoglobin 14.0 gm.; Mantoux tuberculin test 1:1000 negative. Chest x-ray film showed a well-defined rounded mass about 6 cm. in diameter in the medial posterior portion of the right lower lobe having a multi-cystic appearance. Bronchography showed good filling of all the bronchi of the right lower lobe with no filling of the cystic areas and no evidence of bronchiectasis. The branches of the posterior basilar bronchi of the lower lobe revealed arcuation of their normal course due to pressure by the extra-bronchial mass. Laminograms demonstrated that the mass was sharply delineated, most clearly seen at 5 to 8 centimeters from the table-top with the patient supine. A gastrointestinal series was negative with no evidence of hernia. Angiocardiography failed to opacify the mass; an aberrant blood vessel could not be demonstrated. Bronchoscopy showed hyperemia of the right lower lobe bronchus with a moderate amount of white mucopurulent secretion in the basilar branches.

The diagnosis of pulmonary sequestration was suggested on the basis of the history of repeated upper respiratory infections and recent hemoptysis in a young person with no evidence of tuberculosis and with radiographic evidence of a cystic mass in the right lower lobe which on bronchography did not communicate with the bronchial tree but displaced some of the basilar branches.

At operation, the diagnosis of sequestration of a portion of the right lower lobe was confirmed and the right lower lobe was resected. The sequestrated mass was in the posterior medial aspect of the right lower lobe with a large aberrant artery arising from the thoracic aorta just above the diaphragm and entering the sequestrated segment through the leaves of the inferior pulmonary ligament. Examination of the resected lower lobe revealed an irregular rectangular area, in its posterior inferior portion, which was firm and rubbery to palpation and appeared almost completely non-aerated. The regional bronchi were injected with methylene blue and none of the dye entered the mass. On section, this mass showed no recognizable normal lung parenchyma but contained cystic spaces of various sizes. The mass was not encapsulated but was sharply demarcated from surrounding well-aerated normal appearing lung parenchyma. The aberrant artery leading to this segment was injected with fuchsin and its small branches could be seen lying within the fibrous strands between the cystic areas.

DISCUSSION

Intralobar pulmonary sequestration represents a complete developmental separation of a portion of a lobe of a lung from its normal bronchial tree. In early fetal life the lungs extend so rapidly into the enlarging pleural cavities that in embryos of 30 mms. the definitive lobes and fissures are already established.[2] Intralobar developmental anomalies occur before this stage is reached. There is considerable speculation as to whether the mode of origin of the anomalous artery is responsible for, or is secondary to, the pulmonary sequestration. Bemki[1] observed that ectopic tissue may obtain vascular supply from the vicinity if malformation occurs early enough in the embryonic

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FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Postero-anterior chest film showing a localized zone of increased density at the right base, medially.—*Figure 2:* Antero-posterior tomogram, 7 cm. above the table-top, showing the posterior location of the mass which contains multiple lucencies.—*Figure 3:* Right lateral bronchogram, showing normal filling of the bronchial tree and arcuation of the posterior basilar branches by the mass.

development. Wail et al.,[7] on the basis of this observation, favor the concept that sequestration results from "fractioning" of part of the development lung buds; subsequently the separated fraction seeks its own blood supply. Pryce[4, 5] considers the pulmonary anomaly secondary to the vascular anomaly which in turn results from the persistence of one or more of the connections between the dorsal aorta and the post-bronchial pulmonary plexus. These persisting arterial connections cause separation of some of the developing lung buds by traction. Pryce is of this opinion mostly because cases have been encountered in which an anomalous artery from the aorta supplies one or both lower lobes, without any evidence of other abnormalities. Occasionally extra-lobar sequestration occurs in which the anomalous non-functioning portion of pulmonary tissue is found between the diaphragm and the lower lobe, enclosed in a pleural sheath of its own.[8]

The sequestrated lung tissue is usually well demarcated from adjacent lung parenchyma. It may be composed chiefly of normally differentiated lung, a solid mass of branching bronchi, or a multicystic mass. The fact that such cysts sometimes contain air suggests the probability of communication with the bronchial tree.[6] However, injection of dyes into the bronchi of resected specimens has not demonstrated any communication with the abnormal tissue.

Microscopically the picture is variable, with pseudostratified, cuboidal columnar epithelium, mesehchymal elements, irregular dilated cysts, and scattered cartilaginous and fibrous tissue.[7] In about 85 per cent of all cases found in the literature the anomalous artery arises from the lower part of the thoracic aorta. In the remaining 15 per cent the anomalous vessel arises from the upper part of the abdominal aorta or from one of the branches of the celiac axis. This aberrant artery differs histologically from the pulmonary artery in that it has a thicker wall with more muscle fibers and larger elastic fibers.[7] The venous drainage is to the normal pulmonary venous system.[2]

The diagnosis of intralobar pulmonary sequestration should be considered whenever, on x-ray film examination, there is a sharply demarcated multi-cystic density in either lower lobe. A tapering projection may be directed toward the aorta. The distribution of the lesion is not segmental. Although the great majority of cases have been in the posterior medial portion of one of the lower lobes, cases have been reported in a somewhat different anatomic location, such as in the superior segment of the right lower lobe.[6] The walls of the cysts are usually thin and are not always well visualized. Bronchography reveals displacement of some of the bronchial branches and failure of the opaque material to enter the region of the lesion even if cysts with air-fluid levels are present. In addition bronchography helps to rule out bronchiectasis and demonstrates the mass as extra-bronchial. The lesion can simulate a neoplasm. However, this anomaly usually is discovered before the age of 30 years. In the differential diagnosis, herniation through the Bochdalek foramen should also be considered and barium studies of the gastro-intestinal tract may be required to exclude this possibility.

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Paroxysmal Tachycardia in Infants and Children: Report of a Case and Review of the Literature

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Washington, D.C.

The infant's pulse rate during the early weeks of life is rapid and unstable in the range of 110-140 beats per minute. With excitement and infection, the pulse rate may rise to 180 beats per minute. However, once the pulse rate exceeds 200 beats per minute, it takes considerable skill to count the rate. Hubbard[1] considers a regular rate of 250 beats per minute diagnostic of a paroxysmal tachycardia in infants and children.

Paroxysmal tachycardia is rare in infancy. When it occurs it is often serious and may prove fatal. In fact according to some[2] the rapid ectopic rhythms are probably one of the causes of sudden death in children and particularly in infants.

The first recorded case of paroxysmal heart activity in a child was described by Buckman[3] in 1892 in a five year old boy. Lewis was the first to describe it in an infant, a three month old boy. Since 1892 approximately 200-210 cases have been reported in the literature. The last review of Jeune[4] in 1955 discribed 180-190 cases with the addition of seven personal cases. Most recent reports have been from Europe.[5, 6] Goldzier[7] in 1955 reported two cases in infants. Seganti[8] 1956 a case in a 40 day old infant. Boe[9] in 1956 reported a case. Hillrich[10] in 1955 reported four cases in infant boys.

Case Report

P. S., an infant girl was the product of a normal full term pregnancy and a spontaneous delivery under epidural anesthesia following 11 hours labor on October 31, 1957. The birth weight was six pounds two ounces. There was no post-natal disturbance. The heart and lungs were described as "normal" at birth. The infant was discharged as a normal newborn, three days after delivery. During the ensuing two weeks, the child was placed on a Similac formula because of milk allergy and otherwise progressed satisfactorily until 14 days of life when at 5:30 P. M. on November 14, 1957 the father noted the sudden onset of paleness and marked shortness of breath after an episode of vomiting following feeding. The father stated that the color of the face and body was pale but not blue, however, the extremities were blue. There was no convulsion or syncopal attack. The family physician was called and discovered "an uncountable heart rate."

At 7:50 P. M. the child was admitted to Georgetown University Hospital. On admission the infant's weight was six pounds 13 ounces, pulse uncountable, respirations 60 to 70 per minute and temperature 97.8° F. She was in extreme respiratory distress, tachypneic, restless and pale with mottled cyanosis of the entire body. The head and neck examination was normal. Examination of the chest revealed marked subcostal retractions and supraclavicular retractions as well as inspiratory rales bilaterally and a regular but uncountable heart rate—no mumurs were heard. Abdominal examination revealed the liver 3 cm. from the right costal margin. There was no pedal edema and the remainder of the physical examination was within nomal limits.

Course: She was treated with oxygen immediately and an electrocardiogram was done (Figure 1) which revealed a supraventricular tachycardia with a rate of 300 beats per minute. Unilateral carotid sinus pressure and occular pressure had no effect. She was then given 0.18 mg. cedilanid intravenously and within 30 minutes the heart rate had reverted to normal sinus rhythm, i.e. 140 beats per minute with a normal electrocardiogram (Figure 2). The cyanosis and respiratory distress cleared rapidly and the liver edge had receded to normal limits in two hours. The child was discharged the following day with a normal sinus rhythm on an oral digitalis medication with no remission to date.

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*Presently at Browning, Montana.

Discussion

Three types of paroxysmal tachycardia are recognized in infants and children: (1) Supraventricular tachycardia—comprising about 75 per cent; (2) Auricular flutter—comprising about 20 per cent of the cases; and (3) Ventricular tachycardia—comprising about 5 per cent—this type is rare below three months of age. There are also three distinct age groups involved: (1) Congenital Type—those cases occurring prior to birth, in utero.[10, 12, 13] These cases are mostly auricular flutter in type;[12] (2) The Infantile Type—those cases occurring under five months of age. Males predominate this group. The third (3) The Juvenile Group—those cases from five months to 15 years. The majority of cases occurs in the second age grouping.[14]

The etiologic factors according to Graham[15] are:

A. Primary or Ideopathic (majority of all cases)
   A high percentage of these are associated with Wolff-Parkinson-White Syndrome.[9]

B. Secondary Causes:
   (1) Infection
   (2) Cardiac Lesions
      (a) Inflammatory Lesions
      (b) Tumors
      (c) Congenital Heart Disease
   (3) Anesthesia and Drugs, e.g., banthine[16]
   (4) Trauma

It is felt by most authors on the subject that in the first four months of life no definite etiologic factors are usually discernible.[14]

Clinically, this is a serious disease in infants that requires prompt treatment owing to the markedly shortened diastolic filling time which sharply decreases the stroke volume thus resulting in the development of frank congestive heart failure.

In an extreme tachycardia—when the auricular rate is over 300 beats per minute and when these beats are conducted through an "efficient" AV node, there results a 1:1 ventricular response. According to Prinzmetal,[5] clinically the combination of a physiologically "competent" auricular musculature and a highly "efficient" AV node is

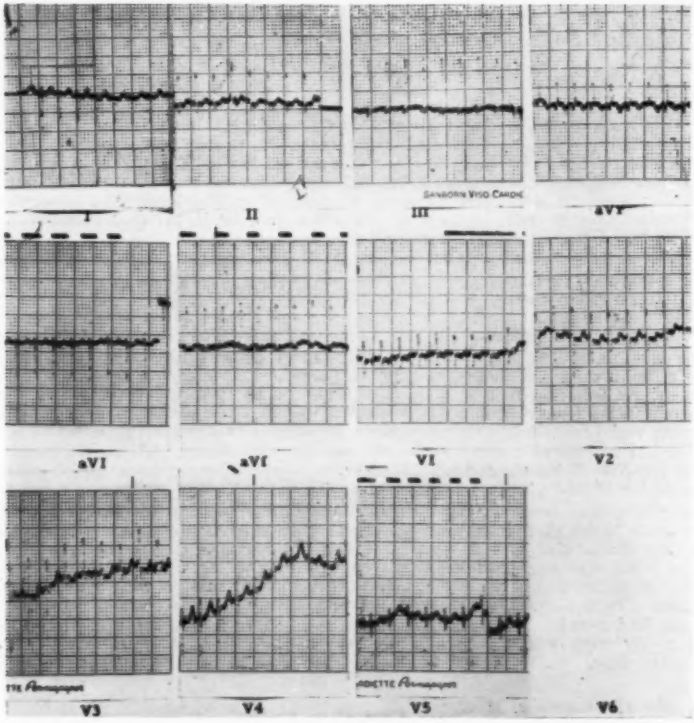

FIGURE 1

undesirable. Failure of these infants to develop fibrillation and A-V block (which would decrease the ventricular rate by 50 per cent or more) results in a marked demand on the infant heart, frequently enough to cause fatal congestive heart failure.

According to Hubbard,[1] a rather consistent clinical syndrome is present. However, this condition is sometimes difficult to recognize and may be detected during an examination for a non-cardiovascular system complaint. Characteristically, the infant becomes restless, with crying, vomiting, and or loose stools. The infant rapidly becomes limp, develpos a dusky, greyish color with obvious prostration. Careful observation reveals the heart beating at an uncountable rate; the peripheral pulses may not be palpable. The heart increases in size and dilates rapidly. Severe dyspnea occurs with a rapid respiratory rate (as high as 150 respirations per minute). The liver becomes engorged and enlarges down to the iliac crest; the spleen also enlarges. There may also be dependent edema and basilar rales and the temperature, if not already elevated, will rise on 102° F. or more.

The ensuing congestive heart failure does not depend so much on the particular rapid rate but rather in the duration of the tachycardia and the age of the patient. The presence of an excessively rapid cardiac rate in a prostrate child suggests the diagnosis and an electrocardiogram will confirm the diagnosis. Once a diagnosis of paroxysmal tachycardia has been made, it is of the utmost importance to rule out the diagnosis of ventricular tachycardia because digitalis, which is the drug of choice in supraventricular tachycardia, is contra-indicated in ventricular tachycardia, where pronestyl is the drug of choice.

The basis of differentiation of the supraventricular and ventricular tachycardia is the width and shape of the ventricular complexes. In supraventricular tachycardias, the complexes are usually normal in outline and similar to normal QRS complexes. In ventricular tachycardias, however, the ventricular complexes are of abnormal outline and quite unlike those present during normal rhythm. However, these criteria do not always hold true and occasionally the exact indentity of the P wave and QRS complexes must be specifically identified.

Treatment consists of giving supportive measures such as oxygen, sedation and antibiotics, if indicated and specific treatment to revert the rapid rate to normal sinus rhythm. This may be accomplished in some cases by increasing vagal tone, i.e. unilateral carotid sinus pressure; occular pressure; induced vomiting; epigastric compression;[5] although both Nadas and Prinzmetal feel that tachycardias at extremely high rates in infants respond less readily to increase in vagal tone. The drug of choice[14] is rapid acting digitalis preparation e.g. cedilanid. The recommended dose is 0.03 mg. per Kg. for the child under two years of age and 0.02 mg. per Kg. for the older child. It is of note that the younger the child, the greater the dosage of digitalis required to produce the adequate effect.[14] There are two methods of giving the medication; on one hand the full dose may be given in one intravenous injection and repeated in two to four hours as necessary[7] or, on the other hand, one half the initial calculated dose is given in one intravenous injection and the remaining one half of the initial calculated dose is given in two divided doses over the next eight hours followed by one sixth of the initial calculated dose every four hours until a remission occurs or toxicity ensues.[14]

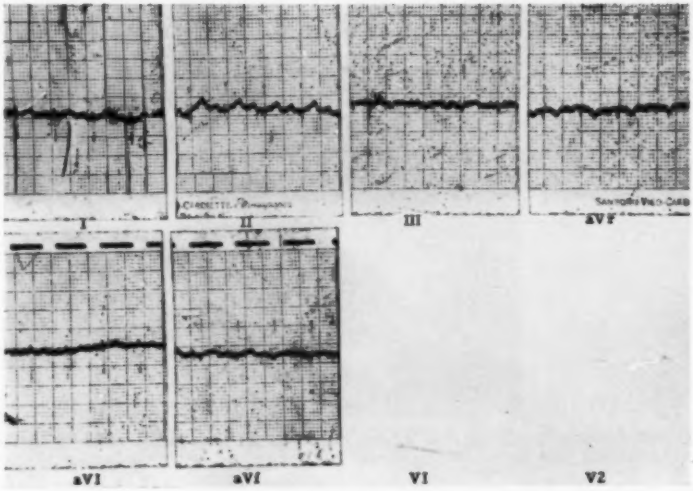

FIGURE 2

If the digitalis fails to induce a reversion of the rate the next drug to be used is quinidine.

The prognosis depends primarily on age, during the attack the younger the child, the greater the likelihood of congestive heart failure. However, following the attack the young infant group generally doesn't tend to have recurrences beyond one year after the initial episode. Older children, on the other hand have a pronounced tendency to recurrences beyond the first year after the initial episode.[12, 17]

It is of note that those children with Wolff-Parkinson-White Syndrome have a marked tendency to recurrence.[17]

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A Left Eparterial Bronchus and a Tri-lobed Left Lung

A CASE REPORT

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Madar, India

Boyden in his excellent book "The Segmental Anatomy of the Lungs" mentions that he and his co-workers had not been able to find a previous report of a left eparterial bronchus in man.

He describes five cases in which this bronchus occurred. In three cases the anterior segment was split by the ectopic left pulmonary artery and in two of these cases there were supernumary clefts. In one case, between the apical and anterior segments on the one hand and the lingula on the other, and in the other case between the apico-posterior and anterior segments on the one hand and the lingula and an abnormal anterior segment on the other. In the fourth case he has described, the eparterial bronchus supplied the apico-posterior segment. In all these four cases, however, the eparterial bronchus appears to arise from the left upper lobe bronchus and not from the main bronchus. In the fifth case described the eparterial bronchus supplies the apico-posterior and a part of the anterior segment and arises from off the main bronchus while the lingula and remaining portion of the anterior segment is supplied by a bronchus which arises from off the left main bronchus in the same position as the middle lobe bronchus on the right.

We wish to report the case of a patient with a left eparterial bronchus in whom the anatomy of the left lung was an exact replica of the normal anatomy of a right lung.

D.S.—This 35 year old man was admitted on December 14, 1957 for treatment of tuberculosis involving the apico-posterior segment of the upper lobe of left lung, first detected in a mass miniature radiographic survey in Delhi in 1953. In January 1956 he developed pleurisy with effusion for which he received 120 grams of streptomycin

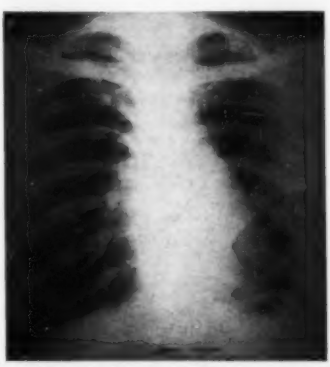

FIGURE 1: P.A. x-ray film of the chest which reveals the abnormal fissure on the left in the second anterior interspace. In this film the heart and the stomach bubble are on the left side.

*Thoracic Surgeon, Madar Union Sanatorium.

and 20 grams of INAH between February 2, 1956 and April 29, 1957. A culture of his sputum at this time was positive for acid fast bacilli and tomographic studies of the left upper lobe suggested the presence of a cavity. He was referred to this hospital for resection of this diseased area.

Physical examination on admission did not reveal abnormality except for an impaired percussion note at the left base with diminished air entry in this region. Routine laboratory examinations were within normal limits. An x-ray film of the chest confirmed the presence of disease in the left upper lobe. An abnormal fissure was seen on the left which was thought to be between the apico-posterior and anterior segments (Fig. 1). During bronchoscopy the left upper lobe orifice could not be visualized due to retraction, only the superior segmental orifice could be visualized by the operator.

On January 21, 1958 a left upper lobectomy was done in the prone position. The pleura was opened through the bed of the sixth rib and was obliterated, the adhesions being easily separated except over the apex where the dissection was carried out in the extra-pleural plane. The major fissure was almost complete and there was a complete fissure between the apico-posterior and anterior segments on the one hand and the lingula segments on the other, resulting in the left lung having three complete lobes. The upper lobe was diseased, the lingula and lower lobes were healthy and it was elected to remove the upper lobe.

The upper lobe bronchus arose above the main pulmonary artery and was supplied by 3 pulmonary arteries which arose from the main pulmonary artery superior and anterior to the bronchus from where one would expect a left trunus anterior to arise (Fig. 2). There was a single vein draining the lobe. The upper lobe bronchus ran posterior to the main pulmonary artery (Fig. 3). There was no other arterial supply to the upper lobe. The lingula bronchus arose from the left lower lobe bronchus opposite the superior segmental bronchus and was supplied by an artery arising from the pulmonary artery opposite the superior segmental artery. The anatomy of the lung in this case was the exact replica of the normal anatomy of the

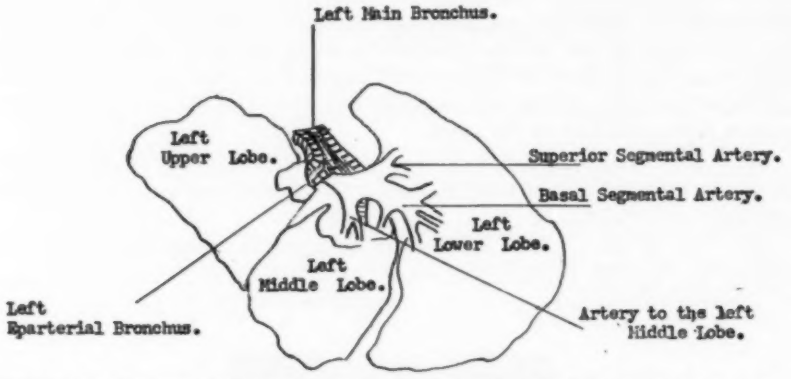

FIGURE 2: Diagram of the operative findings, showing the left eparterial bronchus and the abnormal origin of the lingula bronchus as seen with the patient in the prone position.

FIGURE 3: Diagram showing the origin of the arteries to the left upper lobe. The upper lobe has been retracted posteriorly.

right lung. The position of the heart was normal. The lobe was removed, using the individual ligation technique, the bronchial stump being closed with interrupted catgut sutures—(00 on an atraumatic needle).

The patient had an uneventful convalescence. In May bronchographic studies were carried out which revealed the anatomy of the right lung to be normal (Fig. 4). He was discharged on May 24, 1958.

FIGURE 4: Lateral view of a right bronchogram which reveals a normal distribution of the bronchi to the right lung.

DISCUSSION

Minor variations in the segmental distribution of the bronchi are normal but it is rare to have such a major abnormality. The first thought that comes to mind is whether this patient had a "situs inversus" but the stomach and heart are in their normal position as seen in the plain film of the chest. This latter finding was confirmed at operation. The postoperative bronchogram revealing a normal right lung further negates this possibility and so it must be concluded therefore that this case is a very rare abnormality of the left lung with an eparterial bronchus and a complete horizontal fissure dividing the left lung into three lobes.

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The President's Page

THE PHYSICIAN AND THE LIBRARY

It is axiomatic that there cannot be a great medical school where there is not a great medical library; it is perhaps also true that there cannot be great medicine practiced where great libraries aren't used. Yet how many of us make use of the great medical school libraries which are often found within a convenient distance? How many of us even use the facilities of the medical society locally available?

This is not to suggest that physicians are generally unwilling to spend time "keeping up;" surveys suggest that a very respectable percentage of them spend a great deal of time "keeping up." The question is whether this time is spent wisely. When we read we confine ourselves for the most part to excessively specialized reading. We ordinarily read journals. The number of journals have more than kept pace with the increasing specialization in medicine. Each specialty and each sub-specialty is richly endowed in this respect. One hesitates these days to refer to the old joke about having a separate journal for each side of the heart and one for each of the four chambers; the editor of such a journal might be present.

These journals are of course indispensable to the breath-taking progress of medicine in the twentieth century, but it might be suggested that they are not designed to be **read.** A technical journal is properly a reference work. An overwhelming percentage of the articles published today offer us only bits of information. This information is beyond price when we need it, but to make a habit of reading only such fragments of knowledge is to jeopardize our sense of identity on the one hand and sense of community on the other. At this time especially, when information presses in on us from every side and more and more by the formerly disregarded pharmacological throw-away—what we urgently need is organization.

In other words, we need to become readers of books, and not just books about our particular specialties. The amount of information relevant to the practice of medicine which is available today is simply unassimilatable by any one man; no human being has the intellectual energy which would be required to organize this material in a meaningful fashion. The function of books, simply, is to organize segments of it; sometimes they may work for us simply by giving us ways of looking at a particular aspect of medicine. No book or collection of books can impose on the doctor's experience the unifying vision which is the essence of great medicine. But books make the vision possible. Without books, and a considerable quantity of them, we can be deluged with, and drowned by, the bits of information that we snatch from journals.

The habitual use of a good library is indispensable for this kind of reading. It is a place where one can sample books. One should read the first few chapters of a great many books; one doesn't need to read nearly as many concluding chapters. Few books are for everyone; most books are really for a minority. The problem is to find the books that a particular physician would like to read through and perhaps to own. The library is the place to look for them.

Seymour M. Farber

DR. MOERSCH JOINS COLLEGE STAFF

Dr. Herman J. Moersch, senior consultant in medicine and former chairman of two sections of medicine at the Mayo Clinic, has accepted the post of director of education and research for the American College of Chest Physicians. He will assume his new position after his retirement from the Mayo Clinic on April 1, 1960. Among his many duties will be the coordination of the activities of the 88 councils and committees of the College and the supervision of the research program. He will also serve as the director of the Research and Education Foundation for Chest Disease, an affiliate of the American College of Chest Physicians.

Dr. Moersch was born in St. Paul, Minnesota, on March 14, 1895. He received his academic and medical education at the University of Minnesota and served his internship in the City and County Hospital in St. Paul, Minnesota. He entered the Mayo Clinic in July, 1921, as a fellow in medicine in the Mayo Foundation, which is a part of the Graduate School in the University of Minnesota. He received the degree of master of science in medicine from the University of Minnesota in 1925.

It was during his fellowship at the Mayo Clinic that Dr. Moersch became interested in the fields of pulmonary disease and peroral endoscopy, interests which he has maintained throughout his career. He was appointed a first assistant in medicine in the Mayo Clinic on January 1, 1924. On April 1, 1938, he was named head of a section of medicine in the Mayo Clinic, and on January 1, 1948, he was appointed chairman of two sections of medicine concerned primarily with diseases of the chest. In 1958 he became a senior consultant in medicine.

Dr. Moersch was appointed an instructor in medicine in the Mayo Foundation, Graduate School, University of Minnesota, in 1925. He was advanced to assistant professor in 1928, to associate professor in 1933 and to professor in 1947. In 1938 he was certified as a specialist in internal medicine by the American Board of Internal Medicine, Inc.

Dr. Moersch was president of the American College of Chest Physicians in 1956. In 1956 he was elected president of the staff of the Mayo Clinic. He has been president of the American Bronchoesophagological Society, the American Gastroscopic Society and the Minnesota Trudeau Medical Society. Other associations of which he is a member are the American Medical Association, the American College of Physicians, the American Association for Thoracic Surgery, the Central Society for Clinical Research, the International Bronchoesophagological Society, the Southern Minnesota Medical Society, the Minnesota Society of Internal Medicine, the Chest Club, the Alumni Association of the Mayo Foundation, Society of the Sigma Xi and the Alpha Kappa Kappa professional medical fraternity.

Dr. Moersch has long been interested in the field of medical education and research. He has published more than 150 papers, chapters and other works in the medical literature. He has been awarded many honors at home and abroad, and at the Fourth International Congress on Diseases of the Chest held in Cologne, Germany, in 1956, he was awarded the Great Cross of Merit by the Republic of West Germany.

Chapter News

NEW YORK STATE CHAPTER

The 20th annual clinical meeting of the New York State Chapter will be held at the Sheraton-Ten Eyck Hotel and Albany Medical Center, Albany, February 17, 18 and 19. The program is as follows:

February 17—Sheraton-Ten Eyck Hotel

8:00 p.m. "Dynamics of the Tubercle" (Film, Pfizer Medical Film Library)

February 18—Albany Medical Center

9:00 a.m. Willard J. Davies, Rockville Centre, Moderator
"Bacteriology of Chronic Pulmonary Disease"
DuMont F. Elmendorf, Jr., Albany
Discussion: William Reidt, Albany
"Industrial Exposure to Chlorine Gas"
Frank C. Maxon, Jr., Albany
Discussion: Arthur Q. Penta, Schenectady
"Pulmonary Problems in Infancy and Childhood"
Harvey W. Kausel, Albany
Discussion: Paul Patterson, Albany; Richard L. Woodruff, Schenectady

2:00 p.m. Alfred S. Dooneief, Mt. Kisco, Moderator
"Pulmonary Manifestations of Esophageal Disease"
Allan Stranahan, Albany; Discussion: John O'Hern, Albany
"A Study of the Respiratory Effects of Prednisone in Diffuse Airway Obstruction," James H. Cullen, Albany
Discussion: Preston W. Reynolds, Schenectady
"Results of Open Heart Surgery at Albany Medical Center"
Ralph D. Alley, Albany
Discussion: John Cincotti, Albany, and William F. Lee, Jr., Saratoga Springs

February 19—

9:00 a.m. Diagnostic Chest Conference—Presentation of Interesting Cases

10:30 a.m. Tour, New York State Laboratory, and Department of Health

CALIFORNIA CHAPTER

The annual meeting of the California Chapter of the College will be held at the Ambassador Hotel, Los Angeles, February 20. Following is the program:

9:00 a.m. Opening remarks—Thomas Wiper, San Francisco, Chapter President
Chairman—Mortimer A. Benioff, San Francisco
"Recent Trends in the Incidence of Pulmonary Emphysema"
John Goldsmith, Berkeley
"Theories on the Etiology of Pulmonary Emphysema"
Donald Edwards, Oak Knoll, California
"Eperimental Production of Emphysema"
Richard McLaughlin, San Francisco
"Some Factors in the Pathogenesis of Pulmonary Emphysema, a Morphologic Study," Robert Wright, San Francisco
"A Review of the Environmental, Industrial and Medical Factors in 200 Patients with Emphysema"
Hyman Gierson, Los Angeles
"Erythrocyte and Iron Kinetics in Pulmonary Emphysema"
Myron Pollycove, Berkeley
"New Rebreathing Technique to Estimate Ventilatory Function"
Jack D. Hackney, Loma Linda
"San Diego Soil as a Fomite for Coccidioides Immitis"
Henry A. Walch, San Diego
"Coccidioides Immitis and Immunologic Possibilities"
Abraham M. Breslau, Los Angeles
"Common Misconceptions in Physical Diagnosis Based on Pulmonary Function Tests"
R. Drew Miller, Rochester, Minnesota
Discussion: Hurley L. Motley, Los Angeles

12:00 noon Luncheon, business meeting, presentation of awards
"Cinematography of the Heart Valves in Health and Disease"
Robert P. Glover, Philadelphia

2:00 p.m. Chairman—Marvin S. Harris, Los Angeles
"Cavity Closure in Tuberculosis"
C. Richard Smith, Los Angeles
"A Four-year Evaluation of 46 'Open-Negative' Tuberculosis Patients," Leroy Hyde, Long Beach
"Surgical Aspects of the 'Open-Negative'," Paul C. Samson, Oakland
"The Disappearing AWOL," James Fluvog, Modesto
"Jail X-ray Survey—Analysis of Findings and Follow-up"
G. H. Lambert, Modesto
"Pulmonary Function in Diatomaceous Earthworkers"
Hurley L. Motley, Los Angeles
"Electrode Pacemaker in Surgical Treatment of Complete Heart Block," D. W. Melick, Phoenix
"Cineangiocardiography in Adults," Eugene J. Ellis, Los Angeles
"Surgical Considerations in Coronary Artery Disease"
Robert P. Glover, Philadelphia
"Acid-base Problems in Hypothermia and Perfusion"
John Osborn, San Francisco
Panel discussion: Current Concepts Regarding Cardiac Surgery
Discussors: Eugene J. Ellis, Robert P. Glover, William J. Kuzman (San Diego), D. W. Melick, and John Osborn

Film Program for Annual Meeting

A program of recent films on diseases of the chest will be presented at the 26th Annual Meeting of the College in Miami Beach on Friday, Saturday and Sunday, June 10, 11 and 12, 1960. The Committee on Motion Pictures will be pleased to receive information on new films for possible inclusion in the program. Please send information to Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois. The deadline for receipt of information is February 1.

Motion pictures selected for presentation at the annual meeting will be reviewed by a judging committee and a certificate of merit will be awarded for the best film produced in 1959. Certificates of honorable mention will also be awarded. The College motion picture contest was inaugurated at the 1959 annual meeting in Atlantic City, when first prize was awarded to Dr. JD Mortensen, Latter-Day Saints Hospital, Salt Lake City, for his film "Surgical Repair of Atrial Septal Defect Utilizing the Atrial Well Technique." In addition, four honorable mention awards were presented.

Papers for Vienna Congress

Abstracts of papers for consideration by the program committee for the SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST must be submitted prior to the deadline date of *February 1, 1960*. Abstracts should be typed in English and sent to the executive offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

The Sixth International Congress, sponsored by the Council on International Affairs, American College of Chest Physicians, and presented under the auspices of the Government of Austria, will be held in Vienna, August 27-September 1, 1960. The International Committees of the College will meet in Vienna on Saturday, August 27.

The preliminary program and information concerning post-congress tours will be available in the spring. A registration form may be obtained by writing to the executive offices of the College in Chicago.

Postgraduate Courses in Bronchoesophagology

February 1 to 12, 1960

November 7 to 18, 1960

Courses to be given in the Department of Laryngology and Bronchoesophagology, Temple University Medical Center, under the direction of Drs. Chevalier L. Jackson and Charles M. Norris. Tuition is $250. Application and further information may be obtained by writing to Jackson-Research, Lab 604, Temple University Medical School, 3400 North Broad Street, Philadelphia 40, Pennsylvania.

CALENDAR OF EVENTS

National and International Meetings

26th Annual Meeting, American College of Chest Physicians
Miami Beach, Florida, June 8-12, 1960

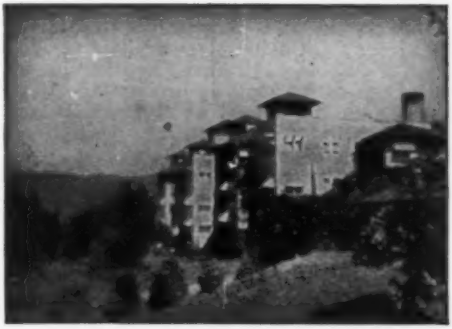
Sixth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Vienna, Austria, August 27-September 1, 1960

Postgraduate Course

13th Annual Course on Diseases of the Chest
Philadelphia, March 14-18, 1960

Chapter Meetings

New York State Chapter, Albany, February 17-19
California Chapter, Los Angeles, February 20
Missouri Chapter, St. Louis, March 13-16
Florida Chapter, Jacksonville, April 10
Texas Chapter, Fort Worth, April 10
Alabama Chapter, Mobile, April 20



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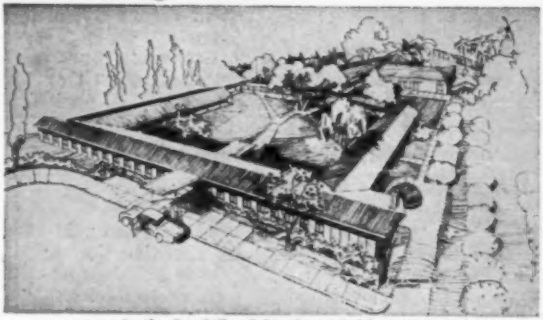

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